Studies and Synthetic Methodology: 1. Cycloaddition of Allylic Azides and Alkynes, 2. Hexafluoro-2-propanol-promoted Friedel–Crafts Acylation Reactions

By

Rakesh Harsukhlal Vekariya

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Chairperson Dr. Apurba Dutta

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Dr. Jeffrey Aubé

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Dr. Brian Blagg

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Dr. Thomas Prisinzano

_____

Dr. Paul R. Hanson

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The Dissertation Committee for Rakesh Harsukhlal Vekariya

certifies that this is the approved version of the following dissertation:

Studies and synthetic methodology: 1. Cycloaddition of allylic azides and alkynes, 2. Hexafluoro-2-propanol promoted Friedel–Crafts acylation reactions

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Abstract

Cycloaddition of allylic azides and alkynes. The 1,3-dipolar Huisgen azide-alkyne cycloaddition is a significant area of interest in modern chemistry. The use of allylic azides as dynamic reaction partners represent a novel variant of this chemistry as they undergo facile 1,3-allylic azide rearrangement, which is also known as the Winstein rearrangement. We combined such an allylic azide rearrangement with an intramolecular Huisgen cycloaddition to afford substituted triazoles in a diastereoselective fashion. Although modest diastereoselectivity was observed in most cases, the majority of diastereomeric pairs were separable. Also, depending on the conditions, a difference in the reactivity of various allylic azides was noticed. Under thermal conditions, vinyl-substituted triazoloxazines were formed, in contrast to copper(I)-catalyzed conditions which afforded dimerized macrocyclic products.

Hexafluoro-2-propanol promoted Friedel–Crafts acylation reactions. The Friedel–Crafts acylation is one of the most important reactions in both academia and industry for the synthesis of aromatic ketones. The reaction is typically promoted by stoichiometric or greater amounts of acids, such as $AlCl_3$, $FeCl_3$, or H_2SO_4, which activate the carbonyl for attack by an aromatic group. A drawback of this extremely versatile acylation reaction is the generation of large amounts of corrosive aqueous waste following post-synthesis workup. We have shown that hexafluoro-2-propanol (HFIP) promotes both intramolecular and intermolecular FC acylation without additional catalysts or reagents. This solvent-promoted acylation is practically simple and accommodates a broad substrates scope. Our preliminary kinetic studies reflects involvement of 3 molecules of HFIP in rate determing step.

Acknowledgments

First and foremost, I would like to thank Professor Jeffrey Aubé for giving me opportunity to work in his group. Jeff's constant support and encouragement throughout my program have been quite helpful. Jeff displays an incredible level of patience as an advisor; it is this quality that has allowed me to succeed under his watch. As I advanced as a graduate student, Jeff let me explore areas of my projects on my own that I found particularly interesting.

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Chapter 1

Combined allylic azide rearrangement and azide–alkyne cycloaddition reaction

1.1 Introduction

Allylic azide rearrangement

In 1960, Winstein and co-workers first reported that allylic azides undergo rearrangement and exist as an equilibrating mixture of regioisomers, specifically they showed that α- and β-methylallylic azides undergo facile rearrangement to give equilibrating mixture of two regioisomers (Figure 1).[1]

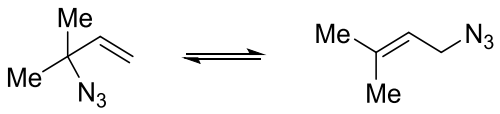


Figure 1. Winstein rearrangement.

Two possible mechanisms for this rearrangement include: 1) a concerted [3,3]-sigmatropic rearrangement (path A, preserves stereochemical integrity of the molecule), 2) an ion-pair formation (path B, leads to loss of stereochemical integrity) (Figure 2).[2]

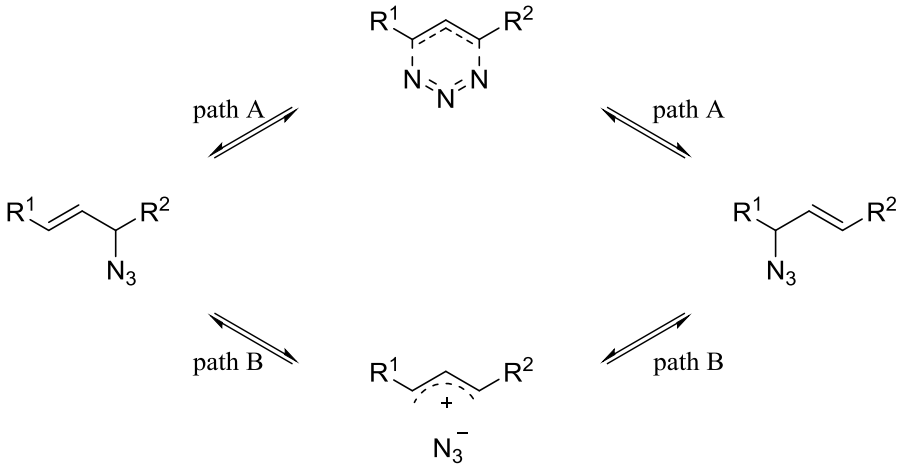
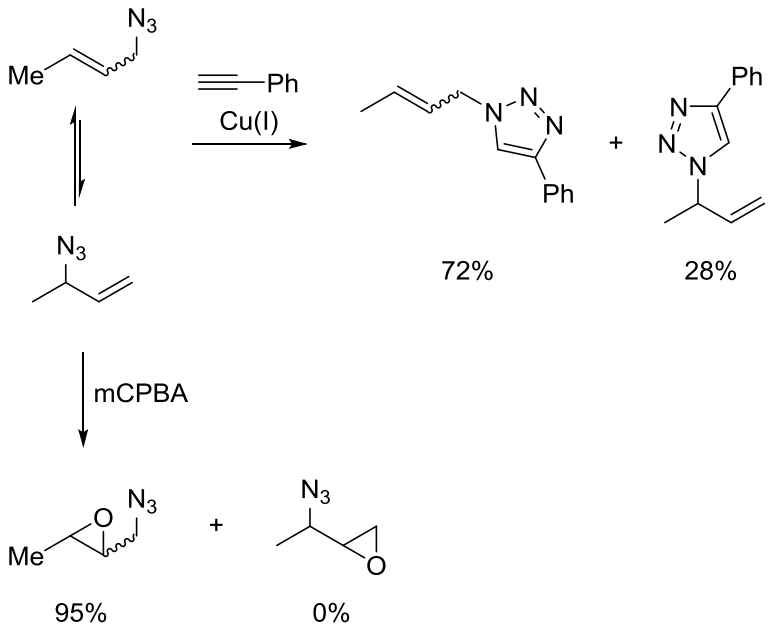


Figure 2. Proposed mechanism of allylic–azide rearrangement.

VanderWerf and Heasley first supported the concerted [3,3]-sigmatropic rearrangement pathway (path A).[3] This was further confirmed by Padwa et al.[2], where during their studies of rhodium catalyzed O-H insertion of carbenoid they observed stereospecific [3,3]-sigmatropic rearrangement of allylic azide in a suprafacial manner. Since the allylic azide rearrangements are facile and generates a mixture of isomers, it has been considered a liability in many cases.[4-8] However, allylic azide rearrangements could be advantageous if one could selectively capture a specific regioisomer arising from rearrangement.[9] In fact, Fokin and coworkers studied the reactivity of allylic azides isomers in Cu(I)-catalyzed azide–alkyne cycloaddition and mCPBA epoxidation of olefins reactions (Scheme 1).[9]

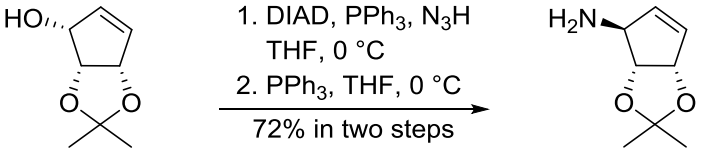
Scheme 1. Allylic azides in Cu(I)-catalyzed azide–alkyne cycloaddition and mCPBA epoxidation reactions[9]



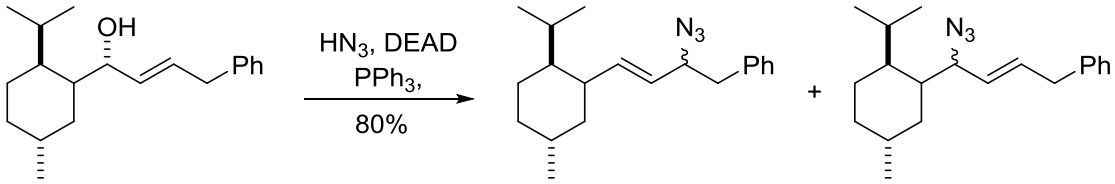
Klepper et al. observed in their synthesis of queuosine that at low temperature they could freeze the rearrangement and capture one isomer by performing a Staudinger reduction at 0 ˚C (Scheme 2a).[10] It has been also reported that one regioisomer of the allylic rearrangement can be stabilized by stericaly bulky group next to allylic azides (Scheme 2b).[11,12]

Scheme 2. Examples toward selective stabilization of one regioisomer of allylic azides[10,11]

a



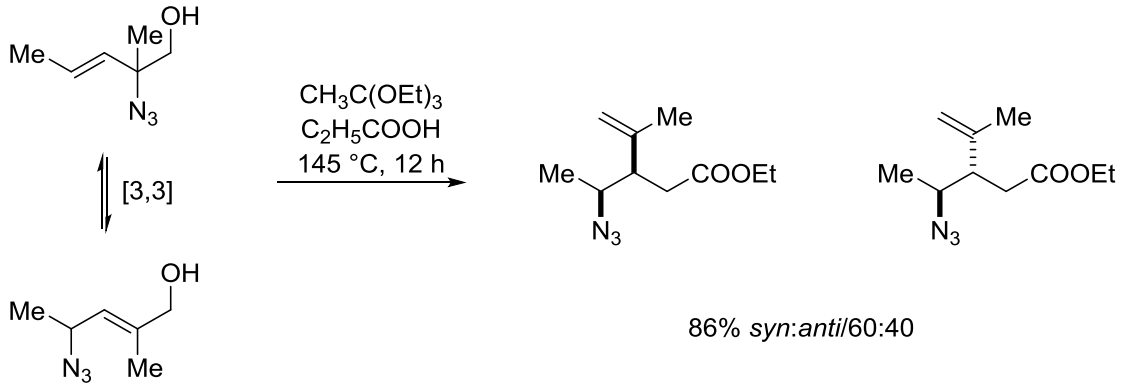
b



98%; β/α = 97/3 2%

Craig and coworkers reported Johnson-Claisen and Ireland-Claisen rearrangements of equilibrating mixture of allylic azides (Scheme 3).[13] They found that irrespective of initial ratio of allylic azides regioisomers, only one regioisomer undergo Claisen rearrangement effectively.

Scheme 3. Claisen rearrangements of allylic azides[13]



86% *syn*:*anti*/60:40

Azide–alkyne cycloaddition

Triazoles are found in many biologically active compounds which possess HIV-1 reverse transcriptase inhibitory activities,[14] antiparasitic,[15] antiplatelet,[16] antimicrobial,[17-21] anticancer,[22,23] antimalarial,[24] and anti-inflammatory activities.[25] One of the most commonly utilized reaction to synthesize triazoles from azides and alkynes is by an azide–alkyne cycloaddition reaction.

Huisgen initially studied azide–alkyne cycloaddition reactions.[26,27] However, the major limitations of Huisgen cycloaddition reaction were high temperature (60-120 °C), long reaction times and the fact that the reaction produced a mixture of regioisomers (1,4- and 1,5-disubstituted 1,2,3-triazoles, Figure 3).[28,29] These limitations were overcome by independent research of Sharpless and Meldal, who reported a copper-catalyzed (Cu(I)) version of the azide–alkyne cycloaddition reaction that selectively produced 1,4-disubstituted 1,2,3-triazoles under mild conditions.[30,31] This is very useful reaction utilized in biomolecular ligation[32] and in vivo tagging[33,34] as well as in polymerization chemistry.[35,36] Subsequently, Fokin and co-workers developed an azide–alkyne cycloaddition catalyzed by a ruthenium(II) ([Cp*RuCl] complexes) that selectively produced 1,5-regioisomers of 1,2,3-triazoles.[37,38]

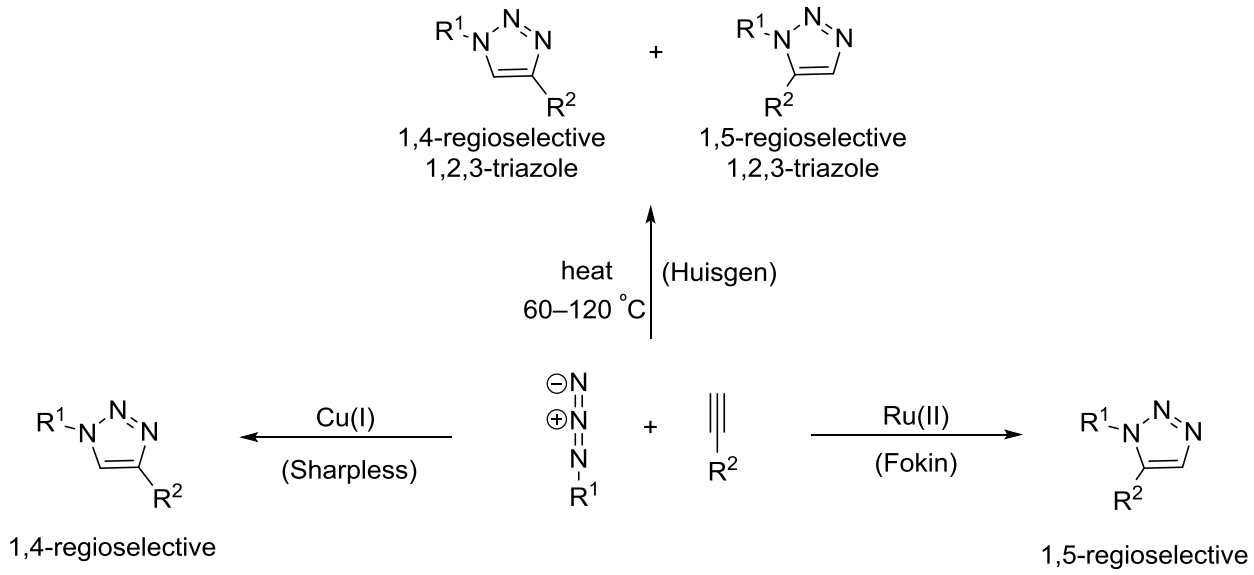


Figure 3. Azide–alkyne cycloaddition.[28]

Combined allylic-azide rearrangement and azide–alkyne cycloaddition

Sharpless and co-workers studied the reactivity of allylic azides in Cu(I)-catalyzed azide–alkyne cycloaddition reactions (Figure 4).[9] They noticed greater selectivity in primary and secondary allylic azides versus tertiary allylic azides where no product obtained from tertiary allylic azides under Cu(I)-catalyzed cycloaddition conditions (Figure 4a-b). However, under these conditions primary versus secondary allylic azides gave the mixture of triazole products similar to that of the starting allylic azides ratio (Figure 4c). Subsequently, Batra and co-workers studied the formation of annulated triazoles from differently substituted allylic azides utilizing thermal intramolecular azide–alkyne cycloaddition conditions.[39]

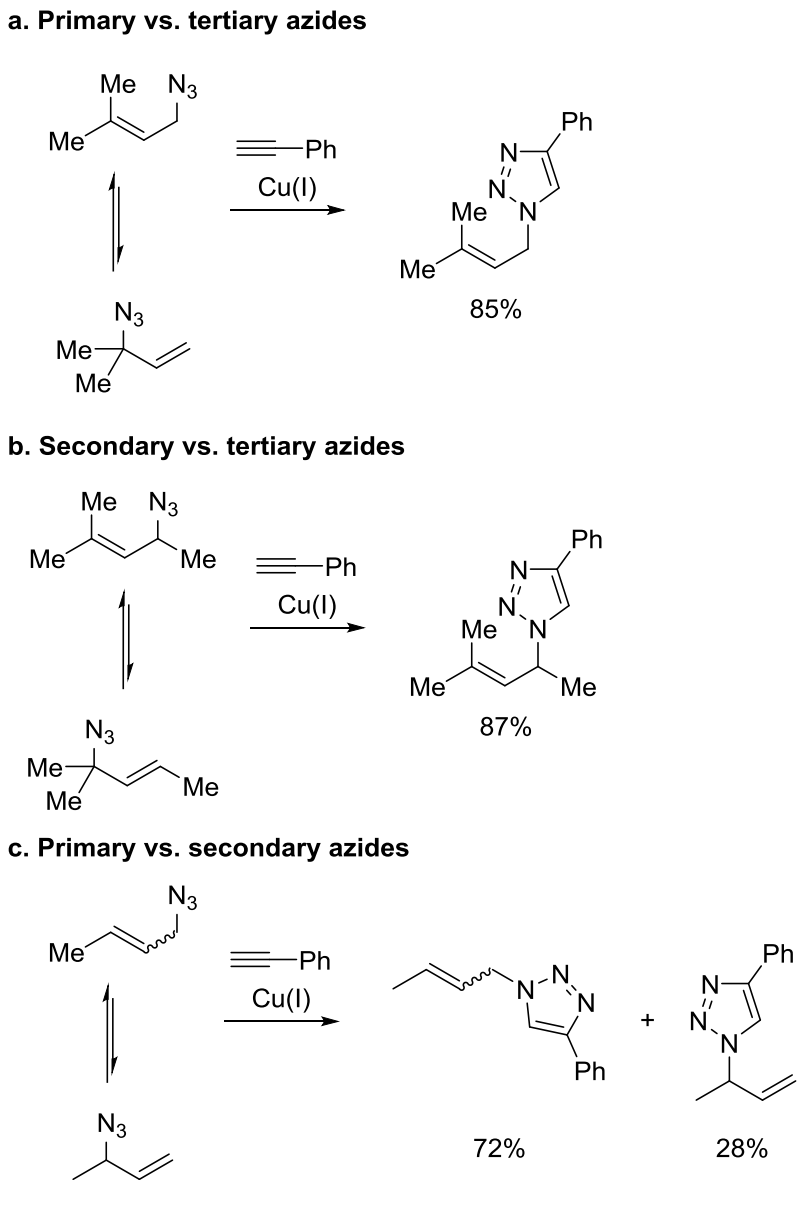


Figure 4. Examples of combined allylic azide rearrangements and azide–alkyne cycloaddition.

Recently, Aubé and co-workers utilized the allylic azide rearrangement in combination with the Schmidt reaction to generate diastereomerically enriched lactam products towards the preparation of useful advanced intermediates in the total synthesis of pinnaic acid (Figure 5).[40]

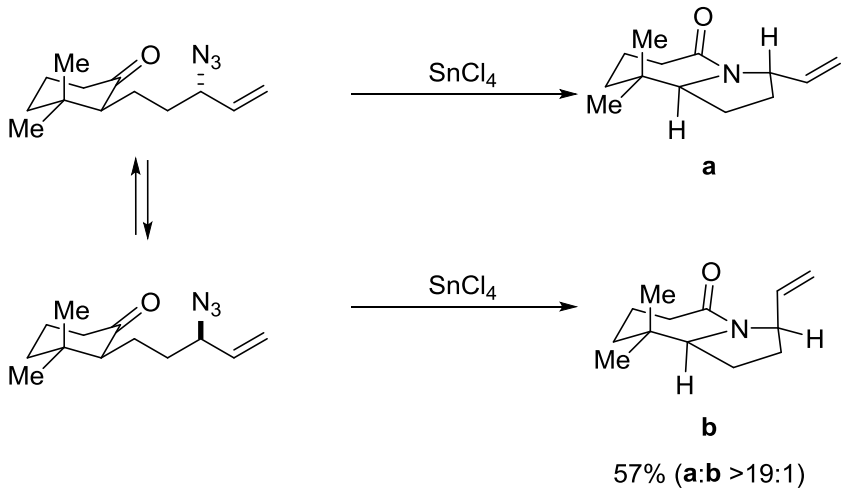


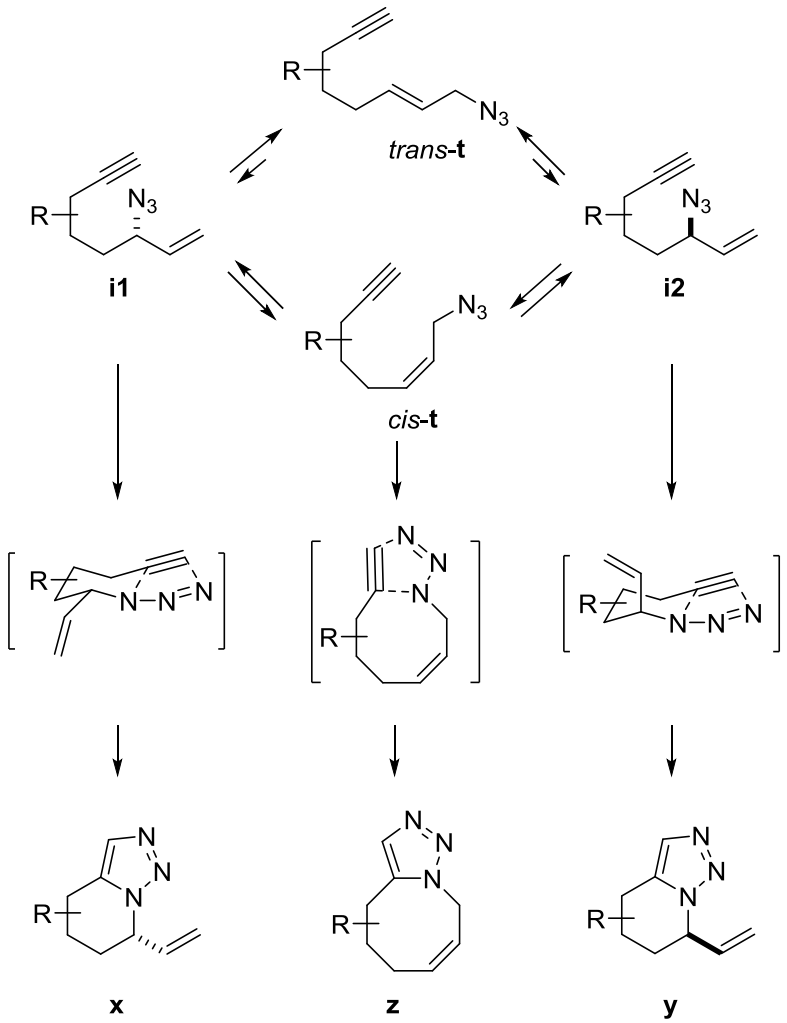
Figure 5. Allylic azide rearrangement and intramolecular Schmidt reaction.

Based on the previous work of the Aubé laboratory, we thought to combine the allylic azide rearrangement with an intramolecular Huisgen cycloaddition reaction focusing on the effects of substrate structure on the product stereochemistry .[41]

An equilibrating mixture of allylic azides (terminal azides *cis*-**t**/*trans*-**t** and internal azides **i1**/**i2**), with already existing stereogenic center, could in theory lead to the formation of three triazole products under thermal cycloaddition condition (Scheme 4). The internal azides **i1** and **i2** would lead to the formation of diastereomers **x** and **y**, respectively. If the equilibrium of allylic azides is rapid compared to cyclization then the ratio of products **x** and **y** would reflect the relative energies of transition states leading to each (one contains an equatorial vinyl group and the other contains an axial vinyl group, assuming that the R group in the tether prefers an equatorial orientation). Furthermore, the **z** product would be obtained from terminal azide *cis*-**t** if the product can accommodate a *cis* double bond in the fused ring system. However, low yield of product **z** would be expected as the *cis* olefin exists in low amounts in equilibrium mixture of allylic azides (generally <10%[9,40]). Additionally, terminal azide *trans*-**t** generated product, containing *trans*

double bond in the fused ring, would not be expected to form due to ring strain. In addition, intermolecular (dimerization) products could arise from any of these isomers.

Scheme 4. Proposed combined allylic azide rearrangement and azide–alkyne cycloaddition

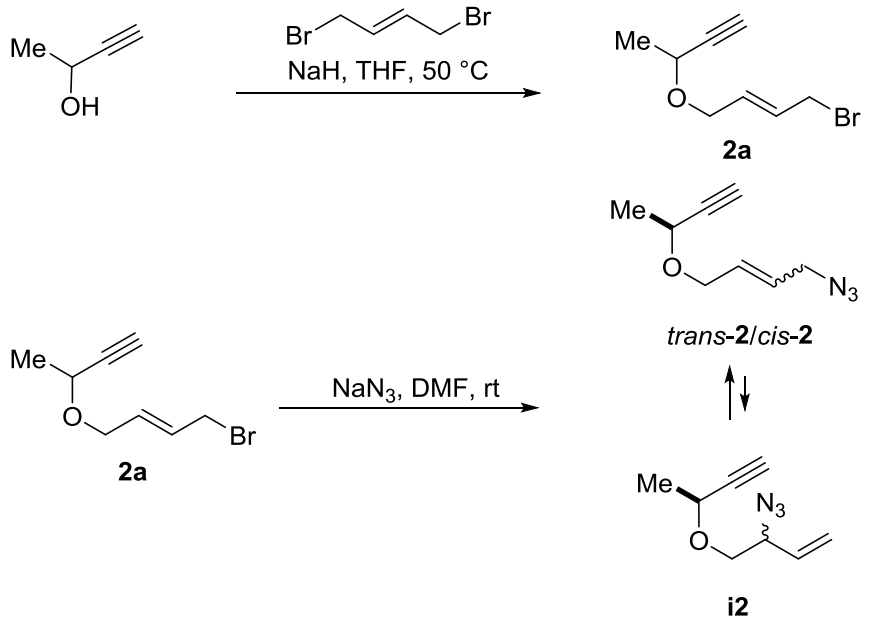


1.2 Results and discussion

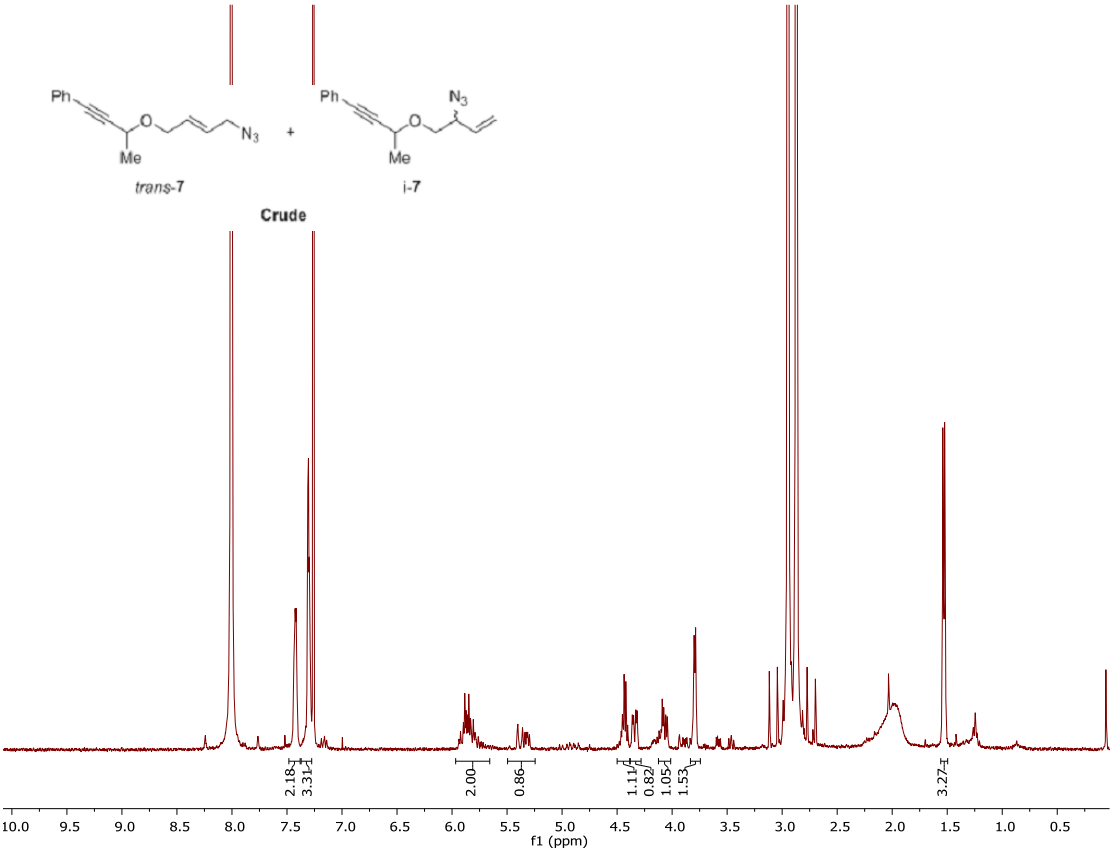
A series of alkynyl azides linked by three-atom oxygen-containing tethers were prepared as shown in Scheme 5. The first step involved alkylation of a propargylic alcohol with 1,4-dibromobutene to obtain an allylic bromide which was then subjected to S_N2 substitution with

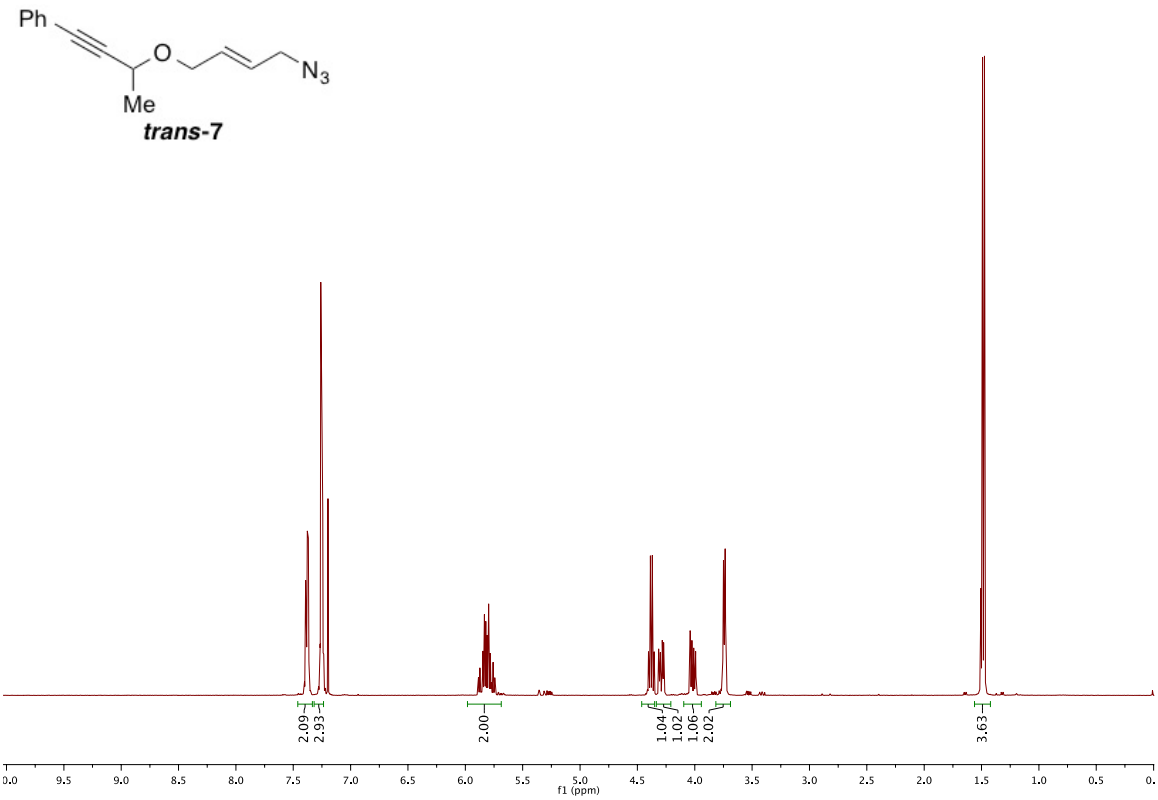
NaN_3. As shown in Scheme 5, each compound was obtained as a mixture of equilibrating allylic azides.

Scheme 5. General route to allylic azides



The mixture of equilibrating azides was then purified by chromatography to give the *trans*-**t** isomer. Based on ^{1}H NMR, most of the isolated azides regained equilibrium in about a week at room temperature. For example compound **7** undergoes rearrangement to give a mixture of isomers. Crude ^{1}H NMR of compound **7** (prepared by azide displacement of the corresponding bromide) reflects all isomers initially observed. Compound **7** was purified by column chromatography to isolate *trans*-**7** which was monitored by ^{1}H NMR at room temperature in $CDCl_3$ for a week. At that point the equilibrium ratio was obtained as no further spectral changes were noticed (Figure 6).


Ph
O
N3
Me
trans-7
+
Ph
N3
O
Me
i-7
Crude
2.18
3.31
2.00
0.86
1.11
0.82
1.05
1.53
3.27
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


Ph
O
N3
Me
trans-7
2.09
2.93
2.00
1.04
1.02
1.06
2.02
3.63
f1 (ppm)

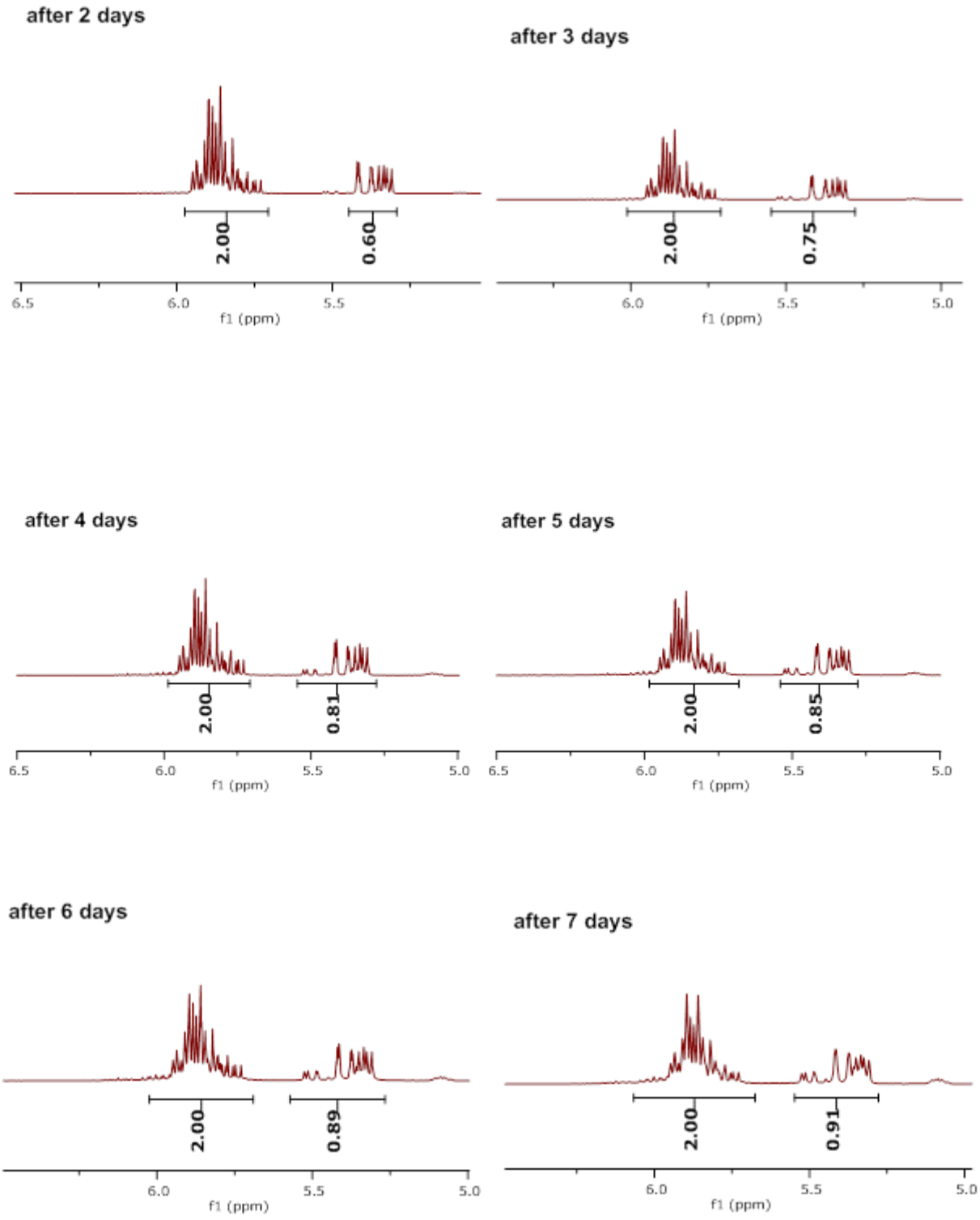
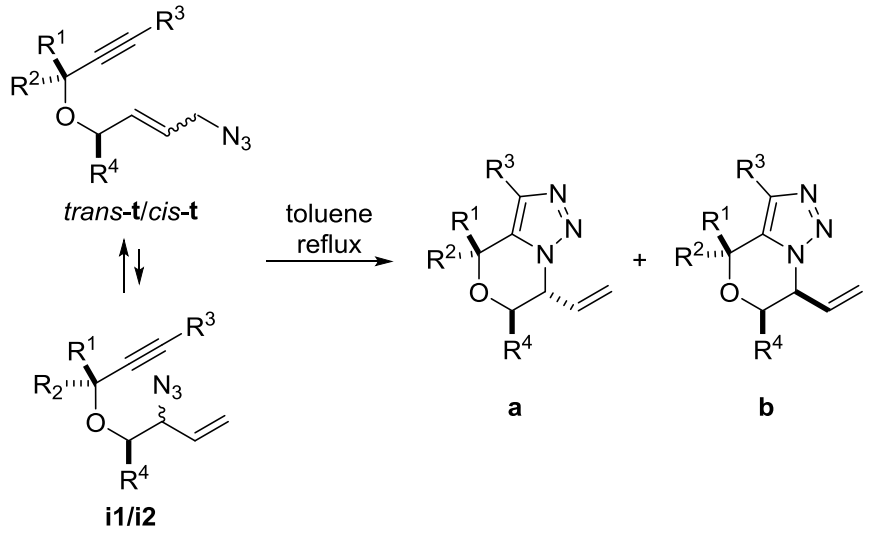


Figure 6. ^{1}H NMR spectras of compound **7** at different time points. Peaks at 5.8 ppm assigned to *trans*-**7** alkenes and peaks at 5.4 assigned to i-**7** alkenes.

Different substituents in azidoalkyne compounds were studied under thermal conditions. The unsubstituted azide **1** upon heating in reflux $CHCl_3$ for 4 h gave **11** in a 72% yield (Table 1, entry 1). The product resulted from cycloaddition of only the internal isomers of allylic azides which was about 17% in the equilibrated mixture of **1**. This result suggested that the rearrangement occurs at a faster rate than azide–alkyne cycloaddition to allow triazole formation from the starting mixture of azides. Azides **2**–**10** were also subjected to similar conditions to obtain corresponding cycloaddition products. In most cases, separable products were obtained with relatively good yields. However, poor diastereoselectivity were observed in all cases (highest being 2:1, Table 1, entry 7). At room temperature compound **2** was reacted to give **12** in about 20 days with similar diastereoselectivity.

Table 1. Intramolecular azide–alkyne cycloaddition of allylic azides[a]



entry	azide (R^1, R^2, R^3, R^4)	ter/int ratio[b]	triazole (yield, %)	dr (a/b)[c]
1	**1** (H, H, H, H)	83:17	**11** (72)	
2	**2** (Me, H, H, H)	67:33	**12** (85)	1.7:1
3	**3** (Ph, H, H, H)	84:16	**13** (83)	1.4:1
4	**4** (Ph, Me, H, H)	64:36	**14** (76)	1.3:1[e]
5	**5** (Me, H, Et, H)	69:31	**15** (93)	1.9:1
6	**6** (Et, H, Me, H)	86:14	**16** (88)	1.5:1
7	**7** (Me, H, Ph, H)	81:19	**17** (84)	2:1
8	**8** (^{i}Pr, H, Ph, H)	74:26	**18** (84)	1.5:1[d]
9	**9** (H, H, H, Me)	88:12	**19** (79)	1:1
10	**10** (H, H, H, Ph)	74:26	**20** (82)	1:1[e]

[a]Conditions: toluene, reflux, 1–2 h (except for entry 1: $CHCl_3$, reflux, 4 h). [b]Equilibrium ratio as determined by NMR analysis of purified allylic azides; compounds attained equilibrium over 1 week at room temperature. [c]Ratio determined by NMR analysis of crude reaction mixtures. [d]The relative stereochemistry of triazoles **18a** and **18b** was confirmed by X-ray crystallography. [e]Inseparable mixture.

The poor diastereoselectivity could be explained using Figure 7. Transition state **B** which has the vinyl group axial could be unfavored because it includes a potential 1,3-diaxial interaction. However, in the observed case the 1,3-diaxial interaction is between vinyl group and an oxygen lone pair which results in small energy difference between the two transition states **A** and **B.** In both cases, R^1 is considered to be equatorial.

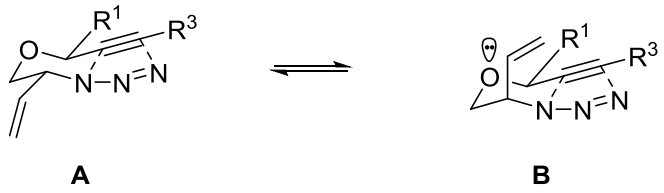
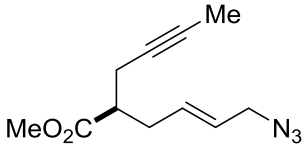
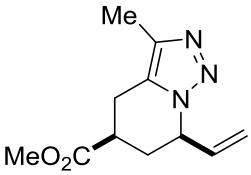
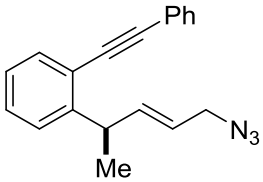
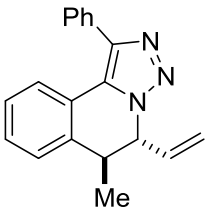
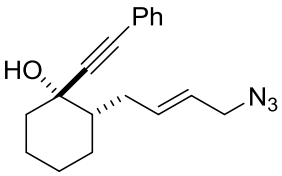
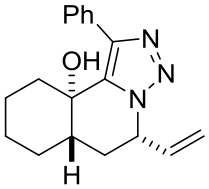
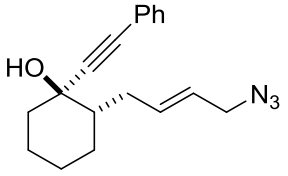
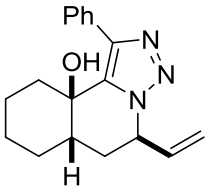
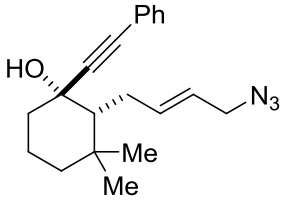
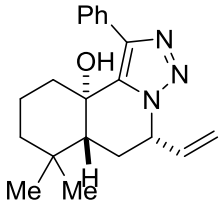


Figure 7. Transition states, with vinyl group equatorial or axial, leading to product isomers **a** and **b**, respectively.

As mono-substituted carbon tether between the azide and alkyne moieties resulted in poor product diastereoselectivity, we thought to explore multi-substituted carbon tethers. Thus, number of azidoalkynes were prepared having all-carbon tethers where the new stereocenter would arise in a 1,2- or 1,3-orientation to an existing center (Table 2). In all cases equatorial transition states were favored but the diastereoselectivity were still modest.

Table 2. Intramolecular cycloaddition of allylic azides and alkynes[a]

Entry	allylic azide (ter:int ratio)	major diastereomer	Yield (%) (dr)[b]
1	 **21** (71:29)	 **25a**	80 (1.5:1)
2	 **22** (85:15)	 **26a**	80 (1.4:1)
3	 **23a** (81:19)	 **27a**	97 (2.9:1)[c]

4	 **23b** (83:17)	 **28a**	96 (6.2:1)[c,d]
5	 **24** (68:32)	 **29a**	73 (2.5:1)[c]

[a]Conditions: toluene, reflux, 2–8 h. [b]Ratio determined by NMR analysis of crude reaction mixtures. [c]The relative stereochemistry of triazoles **27a**, **28a**, and **29a** was determined by X-ray crystallography. [d]Inseparable mixtures.

The results suggest a minor penalty for an axial versus equatorial vinyl group (A-value between 1.49 and 1.68,[42,43] Figure 8a) or a flattened reactive conformation (Table 2, entry 2). Furthermore, we studied the effect of the addition of a ring system in our substrates on the stereoselectivity (Table 2, entries 3-5). In each case, diastereoselectivity was improved compared to previous examples discussed but still remained modest with the highest ratio being 6.2:1 for the formation of **28** (Table 2, entry 4). This result can be explained by a transition state involving 1,3-diaxial interactions between the axial vinyl group and the cyclohexane ring system (Figure 8c). In formation of compound **27**, the minor isomer was disfavored with similar 1,3-diaxial interaction between axial vinyl group and axial hydrogen (Figure 8b).

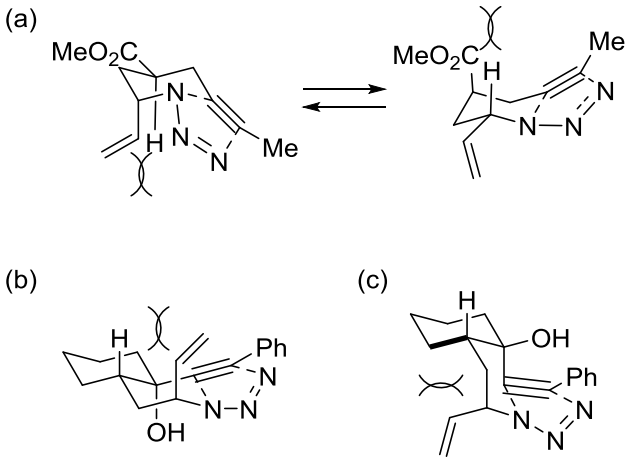


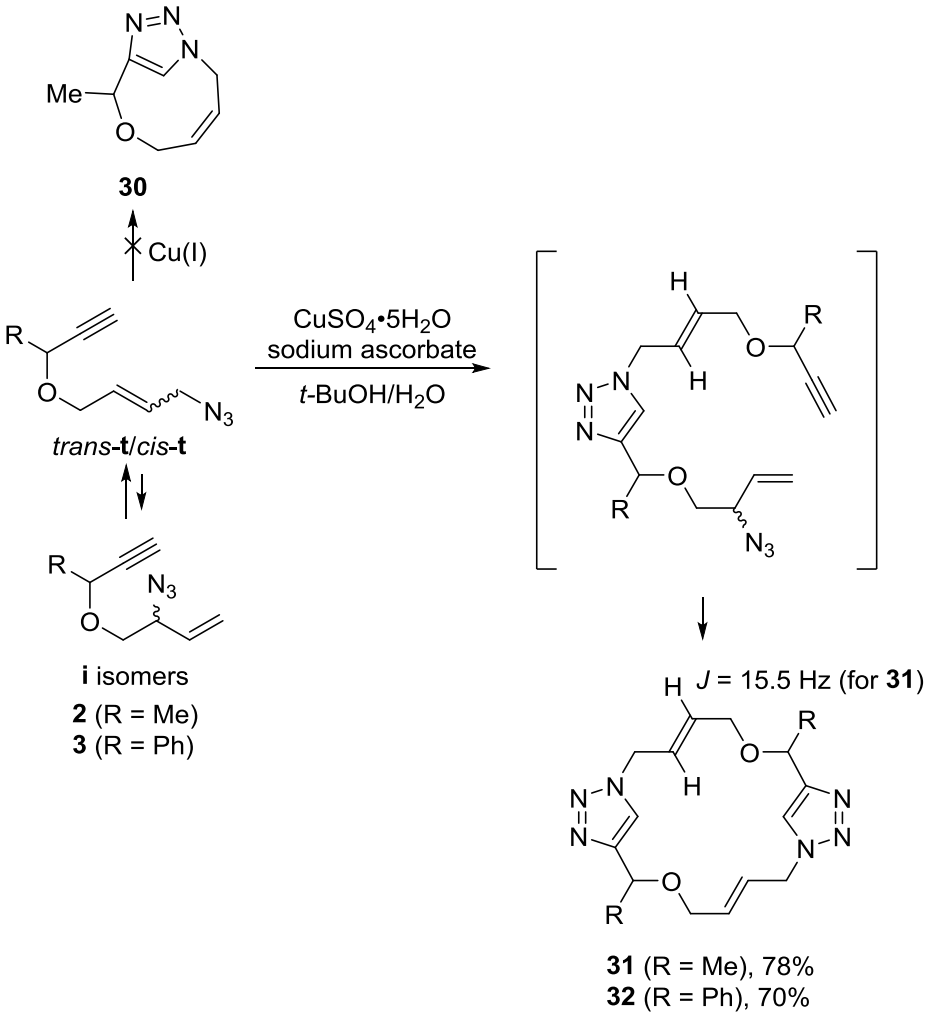
Figure 8. Steric interactions encountered en route to disfavored isomers, specifically compounds (a) **25b**, (b) **27b**, and (c) **28b**.

As noted earlier, ^{1}H-NMR studies showed that the allylic azide rearrangement occurring at room temperature obtained equilibrium in about a week. It was also noted that if a compound possessed terminal alkyne substitution (e.g. compound **7**) no azide–alkyne cycloaddition was observed. In contrast, if the compound had no terminal substitution, azide–alkyne cycloaddition was observed at the slower rate (i.e., about 40% of product formation observed in 6.5 days for compound **1** at that point allylic azide equilibrium was also observed[44]). If we consider the rates to relatively similar at higher temperature then terminally substituted alkyne compounds follow the Curtin-Hammett conditions while compounds with no terminal alkyne substitution follow a mixed kinetic profile, where the barrier for product formation seems close in energy with barrier in allylic azide rearrangement.[45]

Upon treatment with $CuSO_4 \cdot 5H_2O$ compound **2** interestingly gave dimerized azide–alkyne cycloaddition product **31** (Scheme 6, determined by mass spectroscopy). The trans double bond was depicted based on the vicinal coupling constant J = 15.5 Hz in case of compound **31**. While these vicinal protons were coincide in ^{1}H NMR of compound **32**. Thus, for compound **32,** trans double bonds were assigned based on analogy with **31**. In each of these cases only a single set of

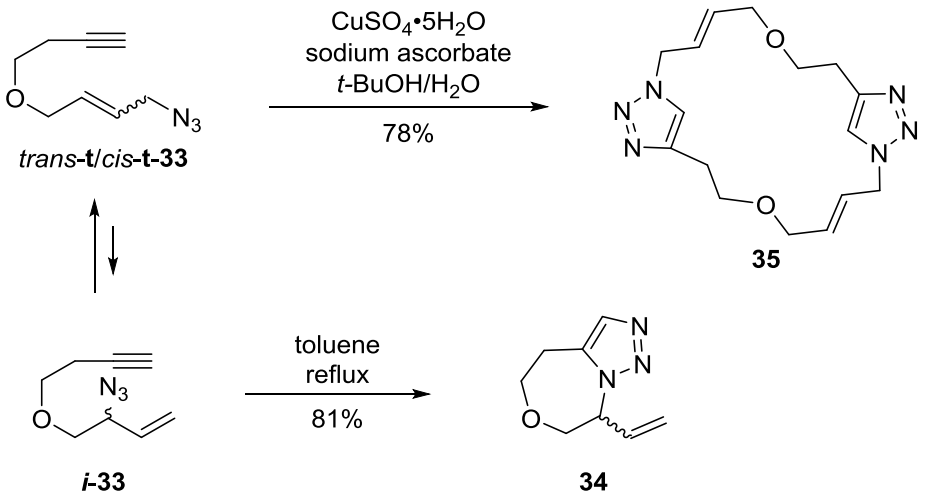
resonances was observed in both the ^{1}H and ^{13}C NMR spectra. Relative stereochemistry could not be assigned with certainty to either product as well as one could not rule out the presence of mixture of stereoisomers. The regioisomer (i.e., 1,4-disubstituted triazole) obtained in both of these cases were in accordance with Cu-catalyzed azide–alkyne cycloaddition reaction outcome.[46,47] Due to strain of the ring system as well as low amount of the *cis*-**t** might have prevented the potential formation of compound **30**. The intermediate shown in Scheme 6 is quite possible where the azide–alkyne cycloaddition happens first between two molecules followed by allylic azide rearrangement and macrocyclization.

Scheme 6. Copper catalyzed azide–alkyne cycloaddition



The allylic azide **33** gave oxazepine **34** under thermal conditions while under the copper(I) catalyzed condition the same azide resulted in macrocyclic triazole **35** (Scheme 7).

Scheme 7. Reactivity under different conditions.

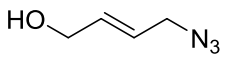


1.3 Conclusions

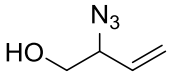
In conclusion, interesting heterocycles were synthesized by an intramolecular Huisgen cycloaddition of an interconverting allylic azide isomers under thermal conditions. The products contain an alkene moiety which can be used as handle for further modification. However, stereoselectivity were modest, products were separable in most cases by column chromatography. Surprisingly, under copper(I)-catalyzed conditions, dimerized macrocyclic products were obtained.

1.4 Experimental Section

General information. Reactions were performed under an inert atmosphere (argon or nitrogen) in oven-dried glassware. All chemicals were used as received from commercial source without further purification. TLC was performed using commercial glass-backed silica plates (250 microns) with an organic binder. Visualization was accomplished using UV light or aqueous $KMnO_4$ by heating. Purification was achieved by flash chromatography on a CombiFlash Rf (automated flash chromatography) system. IR spectra were acquired as thin films or solids. All NMR spectra (^1H, ^{13}C, DEPT, COSY, NOESY, HMBC, and HSQC) were acquired on either a 400 MHz or a 500 MHz instrument. Chemical shifts are reported in parts per million (ppm) and are referenced to the center line of the solvent (δ 7.26 and 2.50 ppm with respect to $CDCl_3$ and DMSO-d_6 for ^1H NMR and δ 77.16 and 39.52 ppm with respect to $CDCl_3$ and DMSO-d_6 for ^{13}C NMR, respectively). Coupling constants are given in Hertz (Hz). HRMS data were collected with an electrospray ion source (ESI). Allyl bromide intermediates were failed to give HRMS. Melting points were determined on an automated melting point apparatus and are uncorrected.



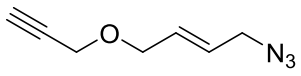
trans-**1a**



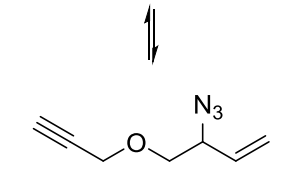
i-**1a**

(*E*)-4-Azidobut-2-en-1-ol (*trans*-**1a**), 2-azidobut-3-en-1-ol (i-**1a**). To a solution of 2-vinyloxirane (370 mg, 5.28 mmol) and ammonium chloride (1.41 g, 26.4 mmol) in a mixed solvent of ethanol (16 mL) and water (2 mL), was added sodium azide (3.43 g, 52.8 mmol). The resulting

mixture was refluxed for 24 h. After cooling to room temperature, water and dichloromethane were added. After separation, the aqueous layer was extracted with dichloromethane three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (10-20% EtOAc/hexanes) to afford *trans*-**1a** and i-**1a** (280 mg, 47%, 96:4) as a colorless oil. Azides *trans*-**1a** and i-**1a**: R_f = 0.30 (50% EtOAc/hexanes). Azide *trans*-**1a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88-5.96 (m, 1H), 5.73-5.80 (m, 1H), 4.19 (d, *J* = 6.4 Hz, 2H), 3.79 (d, *J* = 6.4 Hz, 2H), 2.28 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 124.1, 62.5, 52.2. Azides i-**1a** (diagnostic peaks only): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85-5.93 (m, 1H), 5.73-5.80 (m, 1H), 5.36-5.43(m, 2H), 2.54 (br, 1H), 3.53-3.57 (m, 1H), 3.63-3.67 (m, 1H), 4.03-4.07 (m, 1H), 5.36-5.43(m, 2H), 5.41 (dt, *J* = 17.2 Hz, 1.2 Hz, 1H), 5.28 (dt, *J* = 10.4 Hz, 1.2 Hz, 1H), 4.34 (br, 1H), 3.40 (dd, *J* = 3.6 Hz, 12.3 Hz, 1H), 3.33 (dd, *J* = 7.2 Hz, 12.3 Hz, 1H), 2.08 (br, 1H).



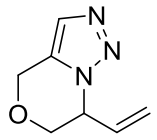
trans-**1**



i-**1**

(*E*)-1-Azido-4-(prop-2-yn-1-yloxy)but-2-ene (*trans*-**1)** and **3-Azido-4-(prop-2-yn-1-yloxy)but-1-ene (**i-**1).** To a solution of a mixture of azides *trans*-**1a**, and i-**1a** (500 mg, 4.42 mmol) in anhydrous DMF (20 mL) at 0 °C under N_2 atmosphere was added sodium hydride (60% in mineral oil, 221 mg, 5.52 mmol). After the resulting mixture was stirred at 0 °C for 30 min, propargyl bromide (80% w/w in toluene, 821 mg, 5.52 mmol) was added slowly. The resulting

mixture was stirred overnight, and quenched with saturated aqueous ammonium chloride. Products were extracted with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (0.5-2% EtOAc/hexanes) to afford a mixture of azides ***trans*-1**, and **i-1** (60 mg, 34%, 83:17) as a colorless oil. Azide *trans*-**1** and i-**1**: R_f = 0.30 (5% EtOAc/hexanes); IR (neat) 2859, 2100 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_7H_{10}N_3O$ $(M+H)^+$ 152.0824, found: 152.0830. Azide *trans*-**1**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (q, *J* = 4.8 Hz, 2H), 4.17 (d, *J* = 2.4 Hz, 2H), 4.11 (d, *J* = 4.1 Hz, 2H), 3.80 (d, *J* = 4.6 Hz, 2H), 2.46 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.7, 126.6, 79.4, 74.7, 69.0, 57.3, 52.2. Azides i-**1** (diagnostic peaks only): ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 17.3, 10.3, 7.1 Hz, 1H), 5.41 (dt, *J* = 17.1, 1.1 Hz, 2H), 5.36 (dt, *J* = 10.3, 1.0 Hz, 2H), 4.23 (t, *J* = 2.4 Hz, 1H), 4.10-4.16 (m, 1H), 3.65 (dd, *J* = 9.9, 4.4 Hz, 1H), 3.55 (dd, *J* = 9.9, 7.4 Hz, 1H), 2.48 (t, *J* = 2.4 Hz, 1H).

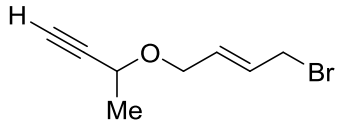


11

7-Vinyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (11). A mixture of azides *trans*-**1**, and i-**1** (32 mg, 0.20 mmol) in chloroform (11 mL) under N_2 atmosphere was refluxed for 4 h. After the reaction was cooled to room temperature, solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (20-50% EtOAc/hexanes) to afford triazole **11** (23 mg, 72%) as a colorless oil. Triazole **11**: R_f = 0.45 (100% EtOAc); IR (neat) 2923 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_7H_{10}N_3O$ $[M + H]^+$: 152.0824, found: 152.0824; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 5.99 (ddd, *J* = 17.4, 10.4, 7.2 Hz, 1H), 5.37-5.47 (m, 2H), 5.06 (q, *J*

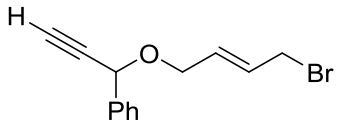
= 6.1 Hz, 1H), 4.94 (s, 2H), 4.12 (dd, *J* = 12.1, 4.3 Hz, 1H), 3.90 (dd, *J* = 12.1, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.3, 130.4, 128.1, 120.7, 68.3, 62.5, 58.6.

Compounds 2a-g were prepared using the following general procedure. 3-Butyn-2-ol (2.0 g, 2.23 mL, 2.85 mmol) was added dropwise via syringe to a suspension of NaH (60% in oil, 1.14 g, 2.85 mmol) in dry THF (25 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and then (*E*)-1,4-dibromo-2-butene (13.41 g, 6.27 mmol) was added and the reaction was heated at 50 °C for 24 h. The mixture was allowed to cool and then quenched with a mixture of Et_2O and H_2O and then poured onto Et_2O and 2M aq HCl. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layer was washed with water (1 × 20 mL) and brine, and dried (Na_2SO_4). Filtration and concentration gave a residue, which was purified by automated chromatography (silica, hexane/EtOAc 9.5:0.5) to give (*E*)-1-bromo-4-(but-3-yn-2-yloxy)but-2-ene (**2a**, 1.82 g, 20%) as a colorless oil.



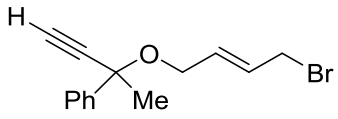
2a

(*E*)-1-Bromo-4-(but-3-yn-2-yloxy)but-2-ene (2a). Obtained as a colorless oil (yield = 31%). R_f = 0.6 (10% EtOAc/hexanes); IR (neat) 3295, 2985, 1648 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (dtt, *J* = 14.0, 7.3, 1.4 Hz, 1H), 5.86 (dddt, *J* = 15.0, 6.0, 5.2, 0.9 Hz, 1H), 4.32 – 4.23 (m, 1H), 4.19 (qd, *J* = 6.6, 2.0 Hz, 1H), 4.01 – 3.94 (m, 3H), 2.43 (d, *J* = 2.0 Hz, 1H), 1.45 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.4, 129.1, 83.6, 73.4, 68.0, 64.8, 32.0, 22.1.



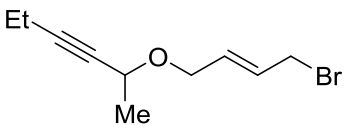
2b

(*E*)-(1-(4-Bromobut-2-enyloxy)prop-2-ynyl)benzene (2b). Obtained as a colorless oil (yield = 30%). R_f = 0.70 (10% EtOAc/hexanes); IR (neat) 3290, 2857, 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (ddd, *J* = 7.6, 1.5, 0.7 Hz, 2H), 7.46 – 7.29 (m, 3H), 6.11 – 5.81 (m, 2H), 5.20 (d, *J* = 2.2 Hz, 1H), 4.26 – 4.17 (m, 1H), 4.17 – 4.05 (m, 1H), 3.96 (dd, *J* = 7.3, 0.8 Hz, 2H), 2.66 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 131.2, 128.7, 128.6, 128.0, 127.5, 84.0, 76.6, 70.9, 67.6, 32.0.



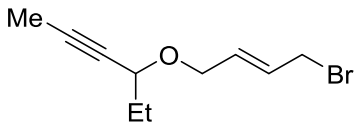
2c

(*E*)-(2-(4-Bromobut-2-enyloxy)but-3-yn-2-yl)benzene (2c). Obtained as a colorless oil (yield = 5%). R_f = 0.7 (10% EtOAc/hexanes); IR (neat) 3291, 2988 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.48 (m, 2H), 7.40 – 7.34 (m, 2H), 7.33 – 7.28 (m, 1H), 6.00 – 5.90 (m, 1H), 5.90 – 5.81 (m, 1H), 4.24 – 4.05 (m, 1H), 4.05 – 3.85 (m, 2H), 3.79 – 3.58 (m, 1H), 2.73 (s, 1H), 1.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 132.0, 128.5, 128.2, 128.1, 126.0, 83.9, 76.2, 75.8, 64.8, 32.9, 32.4.



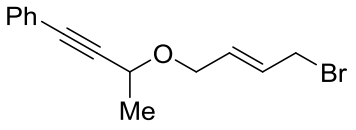
2d

(*E*)-2-(4-Bromobut-2-enyloxy)hex-3-yne (2d). Obtained as a colorless oil (yield = 5%). R_f = 0.70 (10% EtOAc/hexanes); IR (neat) 2981 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 – 5.79 (m, 2H), 4.30 – 4.10 (m, 2H), 4.02 – 3.90 (m, 3H), 2.22 (qd, *J* = 7.5, 1.9 Hz, 2H), 1.41 (d, *J* = 6.5 Hz, 3H), 1.14 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.8, 128.8, 87.4, 79.1, 67.8, 65.2, 32.2, 22.6, 14.1, 12.5.



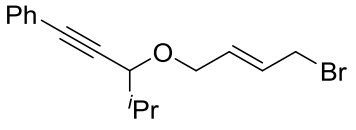
2e

(*E*)-4-(4-Bromobut-2-enyloxy)hex-2-yne (2e). Obtained as a colorless oil (yield = 15%). R_f = 0.70 (10% EtOAc/hexanes); IR (neat) 2969, 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.07 – 5.78 (m, 2H), 4.34 – 4.19 (m, 1H), 4.03 – 3.88 (m, 4H), 1.86 (d, *J* = 2.1 Hz, 3H), 1.79 – 1.61 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.9, 128.7, 82.1, 78.1, 70.9, 67.9, 32.3, 29.2, 9.9, 3.7.



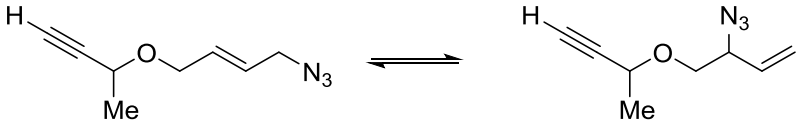
2f

(*E*)-(3-((4-Bromobut-2-en-1-yl)oxy)but-1-yn-1-yl)benzene (2f). Spectral data for compound **2f** was consistent with the literature values.[48]



2g

(*E*)-(3-(4-Bromobut-2-enyloxy)-4-methylpent-1-ynyl)benzene (2g). Obtained as a colorless oil (yield = 11%). R_f = 0.75 (10% EtOAc/hexanes); IR (neat) 2962 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.41 (m, 2H), 7.31 (dd, *J* = 4.0, 2.6 Hz, 3H), 6.20 – 5.77 (m, 2H), 4.39 – 4.31 (m, 1H), 4.13 – 4.02 (m, 2H), 3.98 (d, *J* = 7.3 Hz, 2H), 2.08 – 1.99 (m, 1H), 1.11 – 1.03 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.0, 131.9, 128.7, 128.4, 128.3, 123.0, 87.1, 86.8, 75.4, 68.3, 33.5, 32.3, 18.8, 18.1.

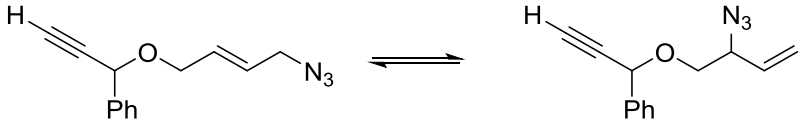


trans-**2** i-**2**

Compounds 2-8 were prepared using the following general procedure. A suspension of (*E*)-1-bromo-4-(but-3-yn-2-yloxy)but-2-ene (**2a**, 1.47 g, 7.23 mmol) and sodium azide (1.41 g, 2.17 mmol) in DMF (40 mL) was stirred for 3 h at room temperature. Saturated aq NH_4Cl was added. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organics washed with water (1 × 20 mL) and brine, and dried over Na_2SO_4. Filtration and concentration gave a residue, which was purified by automated chromatography (silica, hexane/EtOAc 9.5:0.5) to give mixture of azides *trans*-**2**, and i-**2** (0.89 g, 75%, 67:33) as a colorless oil.

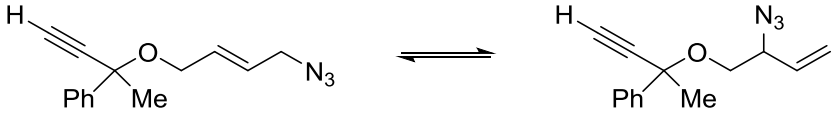
(*E*)-1-Azido-4-(but-3-yn-2-yloxy)but-2-ene (*trans*-2), 3-azido-4-(but-3-yn-2-yloxy)but-1-ene (i-2). Obtained as a colorless oil. *trans*-**2** and i-**2** (67:33): R_f = 0.5 (10% EtOAc/hexanes); IR (neat) 2100 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_8H_{12}N_3O$ $[M + H]^+$ 166.0980, found 166.0976. *trans*-**2**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 – 5.75 (m, 2H), 4.34 – 4.24 (m, 1H), 4.20 (qd, *J* = 6.6, 2.0 Hz, 1H), 4.06 – 3.92 (m, 1H), 3.83 – 3.76 (m, 2H), 2.43 (d, *J* = 2.0 Hz, 1H), 1.46 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.4, 126.3, 83.6, 73.3, 68.2, 64.7, 52.4, 22.1. i-**2** (diagnostic

peaks only): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (d, *J* = 7.4 Hz, 1H), 3.51 (dd, *J* = 10.0, 4.3 Hz, 1H), 3.39 (dd, *J* = 9.9, 8.0 Hz, 1H).



trans-**3** i-**3**

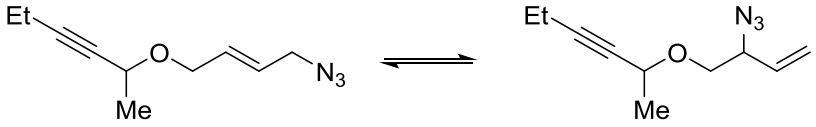
(*E*)-(1-(4-Azidobut-2-enyloxy)prop-2-ynyl)benzene (*trans*-3), (1-((2-azidobut-3-en-1-yl)oxy)prop-2-yn-1-yl)benzene (i-3). Obtained as a colorless oil (yield = 70%). *trans*-**3** and i-**3** (84:16): R_f = 0.6 (10% EtOAc/hexanes); IR (neat) 2097 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}N_3O$ $[M + H]^+$ 228.1137, found 228.1152. *trans*-**3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.47 – 7.30 (m, 3H), 6.03 – 5.74 (m, 2H), 5.22 (d, *J* = 2.2 Hz, 1H), 4.24 (ddt, *J* = 7.2, 5.1, 1.0 Hz, 1H), 4.14 (ddd, *J* = 6.4, 4.8, 0.7 Hz, 1H), 3.80 (d, *J* = 5.5 Hz, 2H), 2.66 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 131.2, 128.8, 128.8, 127.6, 126.6, 81.5, 76.1, 70.8, 67.8, 52.4. i-**3** (diagnostic peaks only): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (ddd, *J* = 13.9, 6.9, 3.4 Hz, 2H), 5.40 (q, *J* = 1.1 Hz, 1H), 5.35 (q, *J* = 1.1 Hz, 1H), 5.33 (t, *J* = 1.1 Hz, 1H), 5.30 (t, *J* = 1.2 Hz, 1H), 3.74 (dd, *J* = 9.9, 4.2 Hz, 1H), 3.69 – 3.60 (m, 2H), 3.55 (dd, *J* = 9.9, 7.7 Hz, 1H), 2.68 (d, *J* = 2.2 Hz, 2H).



trans-**4** i-**4**

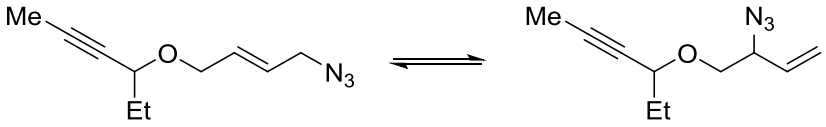
(*E*)-(2-((4-Azidobut-2-en-1-yl)oxy)but-3-yn-2-yl)benzene (*trans*-4), (2-((2-azidobut-3-en-1-yl)oxy)but-3-yn-2-yl)benzene (i-4). Obtained as a colorless oil (yield = 89%). *trans*-**4** and i-**4** (64:36): R_f = 0.6 (10% EtOAc/hexanes); IR (neat) 2101 cm^{-1}; HRMS (ESI) *m/z* calcd for

$C_{14}H_{16}N_3O$ $[M + H]^+$ 242.1293, found 242.1322. *trans*-**4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ .68 – 7.57 (m, 2H), 7.38 (tt, *J* = 6.6, 1.0 Hz, 2H), 7.34 – 7.28 (m, 1H), 5.96 – 5.72 (m, 2H), 4.21 – 4.10 (m, 1H), 3.78 (dd, *J* = 5.9, 1.3 Hz, 2H), 3.75 – 3.66 (m, 1H), 2.74 (s, 1H), 1.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 132.0, 128.5, 128.1, 126.0, 125.3, 83.9, 76.2, 75.8, 64.9, 52.5, 33.0. i-**4** (diagnostic peaks only): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.46 (m, 1H), 3.27 (dd, *J* = 9.7, 4.3 Hz, 1H), 3.18 (dd, *J* = 9.8, 7.9 Hz, 1H).



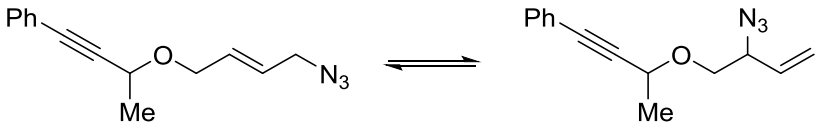
trans-**5** i-**5**

(*E*)-2-((4-Azidobut-2-en-1-yl)oxy)hex-3-yne (*trans*-5), 2-((2-azidobut-3-en-1-yl)oxy)hex-3-yne (i-5). Obtained as a colorless oil (yield = 64%). *trans*-**5** and i-**5** (69:31): R_f = 0.6 (10% EtOAc/hexanes); IR (neat) 2098 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{10}H_{16}N_3O$ $[M + H]^+$ 194.1293, found 194.1302. *trans*-**5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 – 5.72 (m, 2H), 4.32 – 4.22 (m, 1H), 4.18 (qt, *J* = 6.5, 1.9 Hz, 1H), 4.04 – 3.92 (m, 1H), 3.83 – 3.75 (m, 2H), 2.22 (qd, *J* = 7.5, 1.9 Hz, 2H), 1.41 (d, *J* = 6.6 Hz, 3H), 1.14 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.8, 125.9, 87.4, 79.2, 67.9, 65.1, 52.5, 22.6, 14.1, 12.5. i-**5** (diagnostic peaks only): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 – 5.28 (m, 3H), 3.73 (dd, *J* = 10.1, 7.3 Hz, 1H), 3.49 (dd, *J* = 10.1, 4.4 Hz, 1H), 3.37 (dd, *J* = 10.0, 8.0 Hz, 1H), 2.77 – 2.64 (m, 1H).



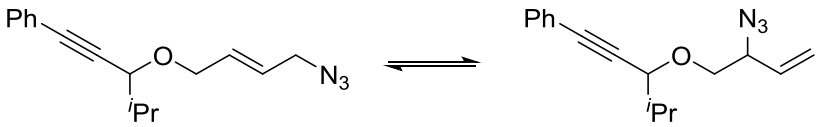
trans-**6** i-**6**

(*E*)-4-((4-Azidobut-2-en-1-yl)oxy)hex-2-yne (*trans*-6), 4-((2-azidobut-3-en-1-yl)oxy)hex-2-yne (i-6). Obtained as a colorless oil (yield = 56%). *trans*-**6** and i-**6** (86:14): R_f = 0.55 (10% EtOAc/hexanes); IR (neat) 2099 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{10}H_{16}N_3O$ $[M + H]^+$ 194.1293, found 194.1288. *trans*-**6**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 – 5.73 (m, 2H), 4.32 – 4.20 (m, 1H), 4.04 – 3.91 (m, 2H), 3.79 (d, *J* = 5.7 Hz, 2H), 1.86 (d, *J* = 2.0 Hz, 3H), 1.79 – 1.61 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.9, 125.8, 82.1, 78.1, 70.8, 68.0, 52.5, 29.2, 9.9, 3.7. i-**6** (diagnostic peaks only): ^1H NMR (400 MHz, $CDCl_3$) δ 5.44 – 5.24 (m, 4H), 3.48 (dd, *J* = 10.0, 4.4 Hz, 1H), 3.36 (dd, *J* = 10.0, 8.0 Hz, 1H).



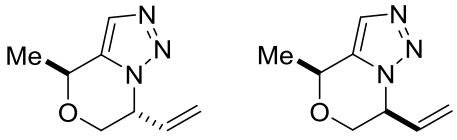
trans-**7** i-**7**

(*E*)-(3-(4-Azidobut-2-enyloxy)but-1-ynyl)benzene (*trans*-7), (3-((2-azidobut-3-en-1-yl)oxy)but-1-yn-1-yl)benzene (i-7). Obtained as a colorless oil (yield = 52%). *trans*-**7** and i-**7** (81:19): R_f = 0.6 (10% EtOAc/hexanes); IR (neat) 2095 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}N_3O$ $[M + H]^+$ 242.1293, found 242.1303. *trans*-**7**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.37 (m, 2H), 7.36 – 7.29 (m, 3H), 6.06 – 5.75 (m, 2H), 4.44 (q, *J* = 6.6 Hz, 1H), 4.35 (ddd, *J* = 13.0, 4.8, 1.1 Hz, 1H), 4.08 (ddd, *J* = 13.0, 5.7, 0.9 Hz, 1H), 3.80 (d, *J* = 5.7 Hz, 2H), 1.55 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.9, 131.6, 128.5, 128.4, 126.2, 122.8, 100.1, 88.9, 85.4, 68.3, 65.4, 52.5, 22.3. i-**7** (diagnostic peaks only): ^1H NMR (400 MHz, $CDCl_3$) δ 5.48 – 5.38 (m, 1H), 5.33 (ddt, *J* = 17.0, 2.2, 1.1 Hz, 2H), 5.30 – 5.23 (m, 2H), 3.83 (dd, *J* = 10, 4.1 Hz, 1H), 3.53 (dd, *J* = 10.0, 4.3 Hz, 1H), 3.41 (dd, *J* = 10.0, 8.0 Hz, 1H).



trans-**8** i-**8**

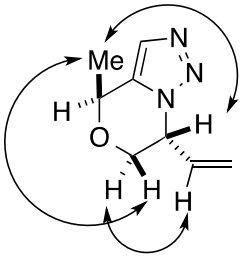
(*E*)-(3-((4-Azidobut-2-en-1-yl)oxy)-4-methylpent-1-yn-1-yl)benzene (*trans*-8), (3-((2-azidobut-3-en-1-yl)oxy)-4-methylpent-1-yn-1-yl)benzene (i-8). Obtained as a colorless oil (yield = 43%). *trans*-**8** and i-**8** (74:26): R_f = 0.65 (10% EtOAc/hexanes); IR (neat) 2099 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}N_3O$ $[M + H]^+$ 270.1606, found 270.1614. *trans*-**8**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (ddd, *J* = 3.7, 2.7, 1.1 Hz, 2H), 7.39 – 7.28 (m, 3H), 6.01 – 5.76 (m, 2H), 4.43 – 4.30 (m, 1H), 4.15 – 4.01 (m, 2H), 3.86 – 3.74 (m, 2H), 2.04 (pd, *J* = 6.8, 5.8 Hz, 1H), 1.07 (dd, *J* = 11.0, 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.9, 131.9, 128.4, 125.8, 123.0, 87.1, 86.7, 75.3, 68.5, 52.5, 33.5, 18.8, 18.1. i-**8** (diagnostic peaks only): ^1H NMR (400 MHz, $CDCl_3$) δ 5.45 – 5.26 (m, 4H), 3.94 (dd, *J* = 9.9, 4.0 Hz, 1H), 3.87 (dd, *J* = 10.0, 7.0 Hz, 1H), 3.58 (dd, *J* = 10.0, 4.4 Hz, 1H), 3.46 (dd, *J* = 10.0, 8.0 Hz, 1H).



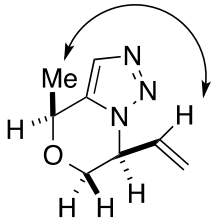
12a **12b**

Compounds 12-18 were prepared using the following general procedure. (*E*)-1-Azido-4-(but-3-yn-2-yloxy)but-2-ene (*trans*-**2**, 0.22 g) was dissolved in toluene (15 mL). The reaction mixture was heated at reflux for 1 h. The solvent was evaporated after cooling the reaction mixture to room temperature. The residue was purified by automated chromatography (silica, hexane:EtOAc/9:1) to give **12a** (0.13 g, 58%) and **12b** (0.06 g, 27%) as a colorless solid.

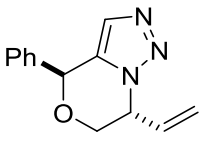
(4*S,7*R**)-4-Methyl-7-vinyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (12a), (4*S**,7*S**)-4-methyl-7-vinyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (12b). 12a**: Obtained as a colorless solid (0.13, 57%). R_f = 0.3 (10% EtOAc/hexanes); mp 82-84 °C; IR (neat) 2985 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_8H_{12}N_3O$ $[M + H]^+$ 166.0980, found 166.0976. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 1.0 Hz, 1H), 5.93 (ddd, *J* = 17.1, 10.3, 7.8 Hz, 1H), 5.66 – 5.45 (m, 2H), 4.98 (dddq, *J* = 9.8, 7.8, 5.0, 1.0 Hz, 1H), 4.89 (qt, *J* = 6.5, 1.0 Hz, 1H), 4.23 (dd, *J* = 12.2, 5.0 Hz, 1H), 3.69 (dd, *J* = 12.2, 10.0 Hz, 1H), 1.57 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.7, 131.2, 128.8, 122.1, 69.4, 68.1, 59.3, 20.4. **12b**: Obtained as a colorless oil (0.62, 28%). R_f = 0.25 (10% EtOAc/hexane); IR (neat) 2973 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_8H_{12}N_3O$ $[M + H]^+$ 166.0980, found 166.0990; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 0.9 Hz, 1H), 6.05 (ddd, *J* = 17.0, 10.4, 6.6 Hz, 1H), 5.35 (ddd, *J* = 10.3, 1.2, 0.7 Hz, 1H), 5.16 (ddd, *J* = 17.1, 1.3, 0.6 Hz, 1H), 5.06 (ddd, *J* = 6.7, 3.4, 1.6 Hz, 1H), 4.90 (qt, *J* = 6.6, 0.9 Hz, 1H), 4.19 (dd, *J* = 12.1, 1.6 Hz, 1H), 4.03 (dd, *J* = 12.1, 3.6 Hz, 1H), 1.58 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.3, 134.4, 128.5, 119.3, 69.3, 67.6, 57.8, 20.7. The indicated NOE correlations were used to assign stereoisomers **12a** and **12b**



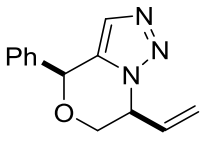
12a



12b

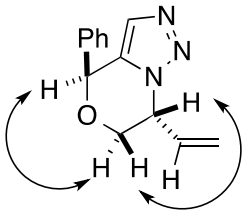


13a

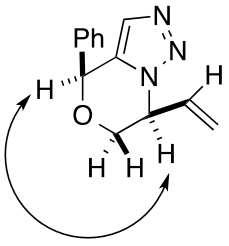


13b

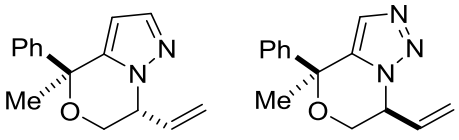
(4*S,7*R**)-4-Phenyl-7-vinyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (13a), (4*S**,7*S**)-4-phenyl-7-vinyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (13b). 13a**: Obtained as a colorless solid (0.06, 46%). R_f = 0.3 (10% EtOAc/hexanes); mp 65-67 °C; IR (neat) 2859, 1454 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}N_3O$ $[M + H]^+$ 228.1137, found 228.1138. ^1H NMR (400 MHz, $CDCl_3$) δ7.46 – 7.38 (m, 3H), 7.38 – 7.32 (m, 2H), 7.31 (d, *J* = 0.7 Hz, 1H), 6.02 (ddd, *J* = 17.3, 10.3, 7.7 Hz, 1H), 5.82 (s, 1H), 5.57 (t, *J* = 13.8 Hz, 2H), 5.20 – 5.08 (m, 1H), 4.32 (dd, *J* = 12.2, 4.9 Hz, 1H), 3.87 (dd, *J* = 12.2, 9.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.7, 134.0, 131.5, 130.6, 129.7, 129.1, 127.9, 122.1, 75.7, 67.8, 59.4, 29.9. **13b**: Obtained as a colorless solid (0.05, 38%). R_f = 0.25 (10% EtOAc/hexane); mp 136-138 °C; IR (neat) 1074 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}N_3O$ $[M + H]^+$ 228.1137, found 228.1137; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.37 (m, 3H), 7.37 – 7.31 (m, 2H), 6.13 (ddd, *J* = 17.0, 10.4, 6.5 Hz, 1H), 5.84 (s, 1H), 5.43 (dd, *J* = 10.4, 0.5 Hz, 1H), 5.35 – 5.25 (m, 1H), 5.22 – 5.12 (m, 1H), 4.20 (ddd, *J* = 15.9, 12.2, 3.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8, 134.1, 129.7, 129.2, 127.9, 119.9, 75.5, 67.3, 58.2, 29.9. The indicated NOE correlations were used to assign stereoisomers **13a** and **13b**



13a

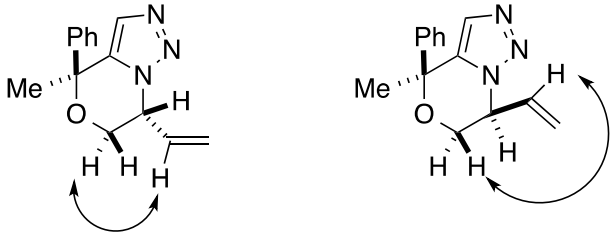


13b

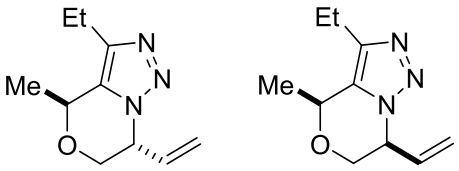


14a **14b**

(4*S,7*R**)-4-Methyl-4-phenyl-7-vinyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (14a), (4*S**,7*S**)-4-methyl-4-phenyl-7-vinyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (14b).** Obtained as a colorless oil (0.07, 76%). R_f = 0.3 (10% EtOAc/hexanes); IR (neat) 2925 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}N_3O$ $[M + H]^+$ 242.1293, found 242.1318. **14a:** ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.40 – 7.28 (m, 5H), 5.88 – 5.70 (m, 1H), 5.58 – 5.43 (m, 2H), 5.01 – 4.97 (m, 1H), 4.00 (dd, *J* = 12.4, 5.3 Hz, 1H), 3.53 (dd, *J* = 12.5, 10.2 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.2, 136.7, 131.3, 130.7, 128.9, 128.5, 125.9, 122.1, 63.8, 57.9, 31.6. **14b**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.39 – 7.29 (m, 5H), 6.12 (ddd, *J* = 17.0, 10.4, 6.6 Hz, 1H), 5.38 (d, *J* = 10.4 Hz, 1H), 5.23 – 5.13 (m, 1H), 5.08 – 5.02 (m, 1H), 3.95 (dd, *J* = 12.4, 1.4 Hz, 1H), 3.88 (dd, *J* = 12.4, 3.6 Hz, 1H), 1.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.1, 136.3, 134.6, 131.0, 128.8, 128.5, 125.9, 119.1, 63.7, 59.3, 31.4. The indicated NOE correlations were used to assign stereoisomers **14a** and **14b**

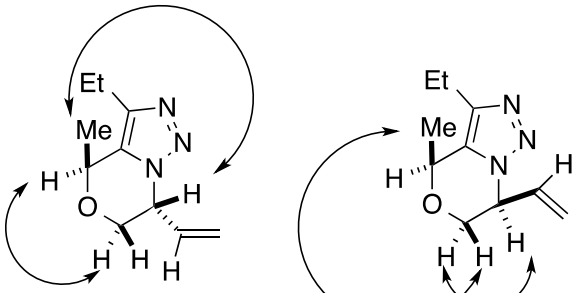


14a **14b**



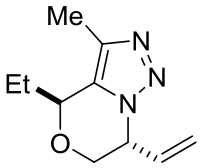
15a **15b**

(4*S,7*R**)-3-Ethyl-4-methyl-7-vinyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (15a), (4*S**,7*S**)-3-ethyl-4-methyl-7-vinyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (15b)**. **15a**: Obtained as a colorless oil (0.03, 63%). R_f = 0.3 (10% EtOAc/hexanes); IR (neat) 2975 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{10}H_{16}N_3O$ $[M + H]^+$ 194.1293, found 194.1299. ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (ddd, *J* = 17.1, 10.3, 7.7 Hz, 1H), 5.56 – 5.43 (m, 2H), 5.06 – 4.86 (m, 2H), 4.17 (dd, *J* = 12.1, 4.7 Hz, 1H), 3.68 (dd, *J* = 12.1, 8.8 Hz, 1H), 2.70 (hept, *J* = 7.3 Hz, 2H), 1.58 (d, *J* = 6.6 Hz, 3H), 1.27 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.4, 131.8, 130.5, 121.4, 69.4, 67.3, 59.4, 19.6, 19.3, 14.1. **15b**: Obtained as a colorless oil (0.01, 30%). R_f = 0.25 (10% EtOAc/hexane); IR (neat) 2975 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{10}H_{16}N_3O$ $[M + H]^+$ 194.1293, found 194.1295; ^1H NMR (500 MHz, $CDCl_3$) δ 6.06 (ddd, *J* = 17.0, 10.3, 6.5 Hz, 1H), 5.42 – 5.31 (m, 1H), 5.27 – 5.17 (m, 1H), 5.01 (dt, *J* = 5.8, 2.8 Hz, 1H), 4.93 (q, *J* = 6.6 Hz, 1H), 4.11 (dd, *J* = 12.1, 2.5 Hz, 1H), 3.97 (dd, *J* = 12.1, 3.6 Hz, 1H), 2.70 (dq, *J* = 12.9, 7.4 Hz, 2H), 1.58 (d, *J* = 6.5 Hz, 3H), 1.28 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.1, 134.1, 130.3, 119.5, 69.2, 67.0, 58.2, 19.8, 19.2, 14. The indicated NOE correlations were used to assign stereoisomers **15a** and **15b**

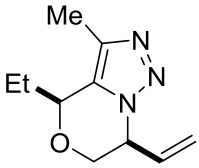


15a

15b



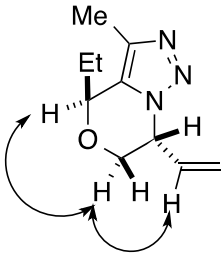
16a



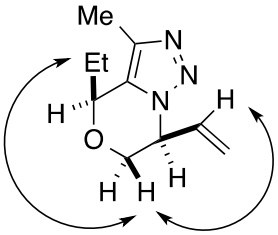
16b

(4*S,7*R**)-4-Ethyl-3-methyl-7-vinyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (16a), (4*S**,7*S**)-4-ethyl-3-methyl-7-vinyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (16b). 16a**: Obtained as a colorless oil (0.09, 56%). R_f = 0.3 (10% EtOAc/hexanes); IR (neat) 2973 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{10}H_{16}N_3O$ $[M + H]^+$ 194.1293, found 194.1291. ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddd, *J* = 17.1, 10.3, 7.7 Hz, 1H), 5.57 – 5.38 (m, 2H), 4.94 (dddd, *J* = 8.9, 7.8, 4.7, 0.9 Hz, 1H), 4.79 (dd, *J* = 7.8, 3.2 Hz, 1H), 4.17 (dd, *J* = 12.1, 4.6 Hz, 1H), 3.66 (dd, *J* = 12.0, 8.9 Hz, 1H), 2.32 (d, *J* = 0.8 Hz, 3H), 2.03 (dqd, *J* = 14.8, 7.4, 3.2 Hz, 1H), 1.86 (dp, *J* = 14.7, 7.4 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.4, 131.7, 130.0, 121.5, 74.0, 67.3, 59.6, 26.0, 11.4, 8.9. **16b**: Obtained as a colorless oil (0.05, 31%). R_f = 0.25 (10% EtOAc/hexane); IR (neat) 2973 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{10}H_{16}N_3O$ $[M + H]^+$ 194.1293, found 194.1292; ^1H NMR (500 MHz, $CDCl_3$) δ 6.04 (ddd, *J* = 17.0, 10.4, 6.5 Hz, 1H), 5.35 (dt, *J* = 10.4, 0.9 Hz, 1H), 5.20 (ddd, *J* = 17.1, 1.4, 0.7 Hz, 1H), 5.05 – 4.96 (m, 1H), 4.80 (dd, *J* = 7.2, 3.2 Hz, 1H), 4.13 (dd, *J* = 12.0, 2.3 Hz, 1H), 3.95 (dd, *J* = 12.0, 3.5 Hz, 1H), 2.31 (d,

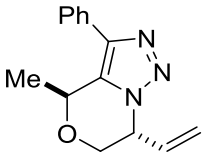
J = 0.8 Hz, 3H), 2.01 (dtd, *J* = 14.8, 7.4, 3.3 Hz, 1H), 1.89 (dp, *J* = 14.6, 7.3 Hz, 1H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.2, 134.2, 129.7, 119.4, 73.8, 66.9, 58.2, 26.1, 11.3, 8.8. The indicated NOE correlations were used to assign stereoisomers **16a** and **16b**



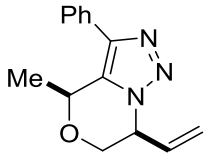
16a



16b



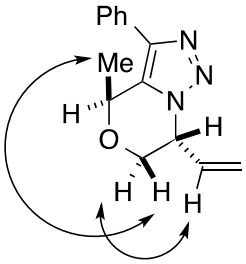
17a



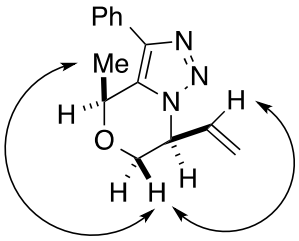
17b

(4*S,7*R**)-4-Methyl-3-phenyl-7-vinyl-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazine (17a), (4*S**,7*S**)-4-methyl-3-phenyl-7-vinyl-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazine (17b). 17a**: R_f = 0.3 (10% EtOAc/hexanes); mp 83-84 °C; IR (neat) 2984, 1607 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}N_3O$ $[M + H]^+$ 242.1293, found 242.1305. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.55 (m, 2H), 7.48 – 7.40 (m, 2H), 7.39 – 7.32 (m, 1H), 6.18 – 5.83 (m, 1H), 5.59 – 5.44 (m, 2H), 5.35 (q, *J* = 6.5 Hz, 1H), 5.21 – 4.95 (m, 1H), 4.22 (dd, *J* = 12, 4.5 Hz, 1H), 3.80 (dd, *J* = 12, 8.0 Hz, 1H), 1.43 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.4, 132.0, 131.36, 131.35, 128.85, 128.23, 127.9, 121.4, 69.8, 66.5, 59.7, 18.8. **17b**: R_f = 0.25 (10% EtOAc/hexane); mp 103-105 °C; IR (neat) 2985, 1492 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}N_3O$ $[M + H]^+$ 242.1293, found 242.1308; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.50 – 7.39 (m, 2H), 7.39 – 7.30 (m, 1H), 6.12 (ddd, *J* = 17.0, 10.0, 6.7 Hz, 1H), 5.49 – 5.40 (m,

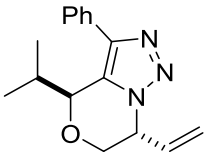
1H), 5.39 – 5.28 (m, 2H), 5.15 – 5.04 (m, 1H), 4.15 (dd, *J* = 12.0, 2.9 Hz, 1H), 4.06 (dd, *J* = 12.0, 3.6 Hz, 1H), 1.46 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.1, 133.7, 131.3, 131.2, 128.9, 128.2, 127.8, 120.1, 69.7, 66.5, 58.7, 19.0. The indicated NOE correlation were used to assign stereoisomers **17a** and **17b**



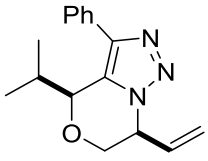
17a



17b



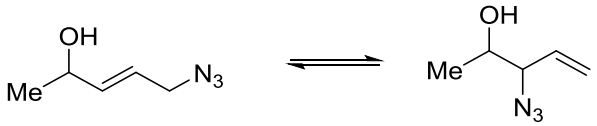
18a



18b

(4*S,7*R**)-4-*iso*-Propyl-3-phenyl-7-vinyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (18a), (4*S**,7*S**)-4-*iso*-propyl-3-phenyl-7-vinyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (18b). 18a**: Obtained as a colorless solid (0.03, 56%). R_f = 0.3 (10% EtOAc/hexanes); mp 160-162 °C; IR (neat) 2969, 1339 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}N_3O$ $[M + H]^+$ 270.1606, found 270.1584. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.53 (m, 2H), 7.45 – 7.40 (m, 2H), 7.38 – 7.33 (m, 1H), 5.96 (ddd, *J* = 17.2, 10.3, 8.0 Hz, 1H), 5.69 – 5.46 (m, 2H), 5.11 (dd, *J* = 2.4, 0.9 Hz, 1H), 5.07 – 4.97 (m, 1H), 4.23 (dd, *J* = 11.9, 4.6 Hz, 1H), 3.68 (dd, *J* = 11.9, 10.0 Hz, 1H), 2.20 (pd, *J* = 7.3, 2.8 Hz, 1H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.55 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 131.6, 131.1, 130.2, 128.8, 128.2, 128.1, 122.0, 77.8, 67.8, 60.5, 29.9, 19.2, 15.1. **18b**: Obtained as a colorless solid (0.01, 29%). R_f = 0.25 (10%

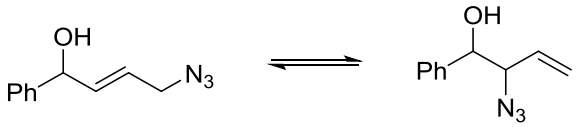
EtOAc/hexane); mp 154-156 °C; IR (neat) 1091 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}N_3O$ $[M + H]^+$ 270.1606, found 270.1609; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H), 7.39 – 7.34 (m, 2H), 7.32 – 7.26 (m, 1H), 6.06 (ddd, *J* = 17.0, 10.4, 6.6 Hz, 1H), 5.42 – 5.20 (m, 2H), 5.03 (d, *J* = 2.4 Hz, 2H), 4.19 (dd, *J* = 11.9, 1.1 Hz, 1H), 3.96 (dd, *J* = 11.9, 3.2 Hz, 1H), 2.18 (pd, *J* = 6.9, 2.4 Hz, 1H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.51 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.1, 134.3, 131.6, 130.0, 128.8, 128.2, 128.0, 119.6, 78.0, 67.3, 58.5, 29.8, 19.1, 15.5. Structures of **18a** and **18b** were defined by single X-ray crystallography.



trans-**3a** i-**3a**

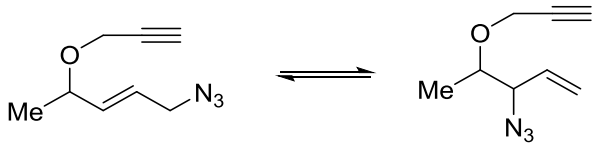
(*E*)-5-Azidopent-3-en-2-ol (*trans*-3a), 3-azidopent-4-en-2-ol (i-3a). To a solution of (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium (Hoveyda-Grubbs 2nd generation catalyst; HG-2) (0.21 g, 0.33 mmol) in CH_2Cl_2 (50 mL) under N_2 atmosphere at room temperature was slowly added a solution of but-3-en-2-ol (7.2 g, 100 mmol) and allyl bromide (300 mmol) in CH_2Cl_2 (10 mL). The resulting reaction mixture was stirred for 3 h. The solvent was concentrated in vacuum and the residue was dissolved in DMSO (10 mL) and DMF (10 mL), followed by addition of NaN_3 (26 g, 400 mmol) at room temperature. After being stirred for 3 h, Et_2O and H_2O were added and the aqueous layer was washed three times with Et_2O. The combined organic layers was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by automated chromatography (silica, hexane/EtOAc 9.5:0.5) to give mixture of *trans*-**3a**, and i-**S3a** (5.64 g, 44%, 57:43) as a colorless oil. *trans*-**3a**: R_f = 0.45 (50% EtOAc/hexanes); IR (neat) 2096 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{10}H_{19}N_6O_2$ $[2M + H]^+$ 255.1569, found 255.1590. ^1H NMR (400 MHz, $CDCl_3$) δ 5.77-

5.86 (m, 1H), 5.64-5.75 (m, 1H), 4.27-4.37 (m, 1H), 3.74 (d, *J* = 5.7 Hz, 2H), 2.46 (br, 1H), 1.23-1.29 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 122.4, 67.7, 52.1, 23.3. i-**3a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 17.2, 10.3, 8.2 Hz, 1H), 5.76 (ddd, *J* = 16.6, 10.6, 8.2 Hz, 1H), 5.44 (d, *J* = 10.1 Hz, 1H), 5.38 (d, *J* = 17.1 Hz, 1H), 5.33-5.40 (m, 2H), 3.86-3.91 (m, 1H), 3.80-3.85 (m, 1H), 3.74 (t, *J* = 7.6 Hz, 1H), 3.63-3.70 (m, 1H), 2.53 (br, 1H), 2.20 (br, 1H), 1.17 (d, *J* = 6.2 Hz, 3H), 1.17 (d, *J* = 6.3 Hz, 3H).



trans-**3b** i-**3b**

(*E*)-4-Azido-1-phenylbut-2-en-1-ol (*trans*-3b), 2-azido-1-phenylbut-3-en-1-ol (i-3b). Obtained as a colorless oil (yield = 28%). *trans*-**3b** and i-**3b** (81:19): R_f = 0.3 (10% EtOAc/hexanes); IR (neat) 2097 cm^{-1}. *trans*-**3b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 5.99 (ddt, *J* = 15.3, 5.6, 1.2 Hz, 1H), 5.85 (dtd, *J* = 15.4, 6.2, 1.3 Hz, 1H), 5.30 – 5.23 (m, 1H), 3.81 (dt, *J* = 6.4, 1.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 137.3, 128.8, 128.1, 126.4, 124.1, 74.3, 52.2. i-**3b** (diagnostic peaks only): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 – 5.61 (m, 2H), 4.73 (d, *J* = 5.2 Hz, 1H), 4.57 (d, *J* = 7.2 Hz, 1H).

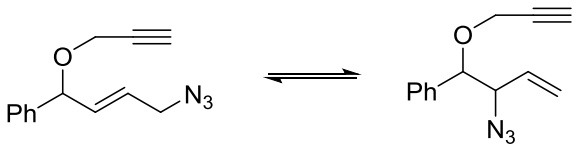


trans-**9** i-**9**

Compounds 9-10 were prepared using the following general procedure. Allylic azides *trans*-**3a** and i-**3a** (1.0 g, 7.86 mmol) were added dropwise via syringe to a suspension of NaH (60% in mineral oil, 0.47 g, 11.7 mmol) in dry THF (40 mL) at 0 °C. The mixture was stirred at 0

°C for 30 min and then propargyl bromide (80 wt % in toluene, 1.86 g, 15.7 mmol) was added and the reaction was stirred at room temperature for 12 h. The reaction mixture was quenched with a mixture of Et_2O and H_2O and then poured onto Et_2O and 2M aq HCl. The aqueous layer was extracted with Et_2O (3 X 10 mL) and the combined organic layer was washed with water (1 × 20 mL) and brine, and dried (Na_2SO_4). Filtration and concentration gave a residue, which was purified by automated chromatography (silica, hexane/EtOAc 9.5:0.5) to give azides *trans*-**9**, and i-**9** (0.44 g, 34%, 88:12) as a colorless oil.

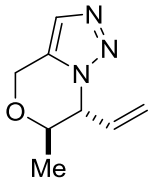
(*E*)-1-Azido-4-(prop-2-yn-1-yloxy)pent-2-ene (*trans*-9), 3-azido-4-(prop-2-yn-1-yloxy)pent-1-ene (i-9). Obtained as a colorless oil. *trans*-**9** and i-**9**: R_f = 0.6 (10% EtOAc/hexanes); IR (neat) 2100 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_8H_{12}N_3O$ $[M + H]^+$ 266.0980, found 266.1000. *trans*-**9**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 – 5.70 (m, 1H), 5.64 (ddt, *J* = 15.4, 7.4, 1.1 Hz, 1H), 4.28 – 3.95 (m, 3H), 3.88 – 3.72 (m, 2H), 2.41 (t, *J* = 2.4 Hz, 1H), 1.29 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 125.8, 80.1, 74.6, 74.2, 6.4, 52.2, 21.5. i-**9** (diagnostic peaks only): ^1H NMR (400 MHz, $CDCl_3$) δ 4.26 (dd, *J* = 3.5, 2.4 Hz, 1H), 4.23 (dd, *J* = 4.7, 2.4 Hz, 1H).



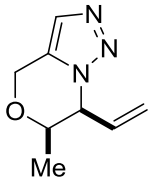
trans-**10** i-**10**

(*E*)-(4-Azido-1-(prop-2-yn-1-yloxy)but-2-en-1-yl)benzene (*trans*-10) (2-azido-1-(prop-2-yn-1-yloxy)but-3-en-1-yl)benzene (i-10). Obtained as a colorless oil (yield = 41%). *trans*-**10** and i-**10** (74:26): R_f = 0.6 (10% EtOAc/hexanes); IR (neat) 2101 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}N_3O$ $[M + H]^+$ 228.1137, found 228.1164. *trans*-**10**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 5H), 5.98 – 5.76 (m, 2H), 5.09 (dd, *J* = 6.3, 1.0 Hz, 1H), 4.18 (dd, *J* = 15.8, 2.4 Hz, 1H),

4.07 (dd, *J* = 15.8, 2.4 Hz, 1H), 3.86 – 3.74 (m, 2H), 2.44 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.63, 135.08, 128.80, 128.33, 127.31, 125.91, 79.97, 79.69, 74.75, 55.53, 52.31. i-**10** (diagnostic peaks only): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61 (d, *J* = 5.6 Hz, 1H), 4.54 (d, *J* = 7.0 Hz, 1H), 4.24 (t, *J* = 2.6 Hz, 1H), 3.93 (d, *J* = 2.4 Hz, 1H), 3.89 (d, *J* = 2.3 Hz, 1H).



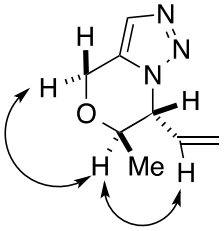
19a



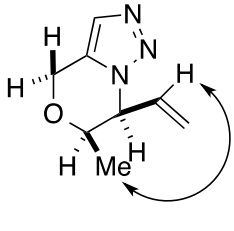
19b

(6*R,7*R**)-6-Methyl-7-vinyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (19a), (6*R**,7*S**)-6-methyl-7-vinyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (19b).** (*E*)-1-Azido-4-(prop-2-yn-1-yloxy)pent-2-ene (*trans*-**9**, 0.43 g) was dissolved in toluene (25 mL). The reaction mixture was heated at reflux for 1 h. The solvent was evaporated after cooling the reaction mixture to room temperature. The residue was purified by automated chromatography (silica, hexane:EtOAc/9:1) to give **19a** (0.16 g, 38%) and **19b** (0.18, 41%) as a colorless oil. **19a**: R_f = 0.3 (50% EtOAc/hexanes); IR (neat) 2984 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_8H_{12}N_3O$ $[M + H]^+$ 166.0980, found 166.1012. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (t, *J* = 0.9 Hz, 1H), 5.83 (ddd, *J* = 17.0, 10.1, 8.6 Hz, 1H), 5.66 – 5.54 (m, 2H), 5.06 (d, *J* = 15.0 Hz, 1H), 4.83 (dt, *J* = 15.1, 1.0 Hz, 1H), 4.55 (t, *J* = 8.9 Hz, 1H), 3.71 (dq, *J* = 9.1, 6.2 Hz, 1H), 1.41 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.7, 130.7, 128.3, 123.3, 74.4, 66.0, 61.8, 17.5. **19b**: R_f = 0.25 (50% EtOAc/hexane); IR (neat) 2985 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_8H_{12}N_3O$ $[M + H]^+$ 166.0980, found 166.1016. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (t, *J* = 0.9 Hz, 1H), 5.89 (ddd, *J* = 17.1, 10.2, 8.1 Hz, 1H), 5.41 (dt, *J* = 10.2, 0.8 Hz, 1H), 5.29 (dt, *J* = 17.1, 1.0 Hz, 1H), 5.08 (dd, *J* = 15.1, 0.8 Hz, 1H), 4.98 – 4.91 (m, 1H), 4.85 (dt, *J* = 15.2, 0.9 Hz, 1H), 4.03 (qd, *J* = 6.5, 3.1 Hz, 1H), 1.34

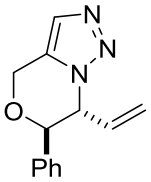
(d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.2, 130.0, 127.9, 121.4, 72.8, 62.6, 62.2, 17.3. The indicated NOE correlations were used to assign stereoisomers **19a** and **19b**:



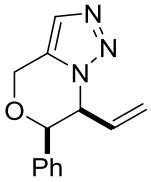
19a



19b

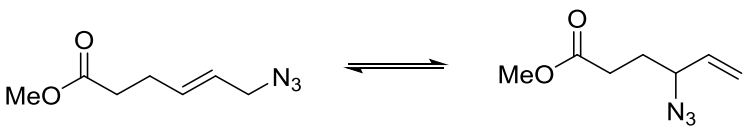


20a



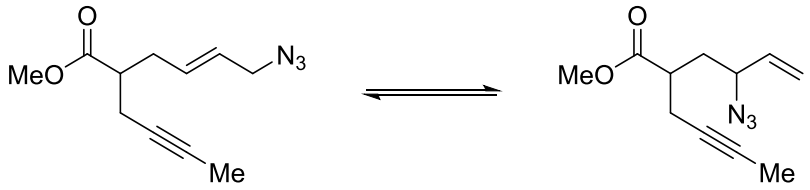
20b

(6*R,7*R**)-6-Phenyl-7-vinyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (20a), (6*R**,7*S**)-6-phenyl-7-vinyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (20b).** Obtained as a colorless solid (yield = 82%; 1:1). **20a** and **20b**: R_f = 0.3 (50% EtOAc/hexanes); IR (neat) 2857 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}N_3O$ $[M + H]^+$ 228.1137, found 228.1171. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.55 (m, 2H), 7.47 – 7.31 (m, 10H), 5.86 (ddd, J = 17.1, 10.3, 8.2 Hz, 1H), 5.66 (ddd, J = 17.0, 10.4, 6.5 Hz, 1H), 5.43 – 5.28 (m, 3H), 5.22 – 5.10 (m, 3H), 5.09 – 4.94 (m, 4H), 4.83 (dt, J = 17.1, 1.0 Hz, 1H), 4.58 (d, J = 9.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.1, 136.1, 130.9, 130.7, 130.6, 130.2, 129.3, 128.8, 128.7, 128.5, 128.4, 128.0, 127.8, 125.9, 123.3, 120.5, 81.1, 78.2, 65.2, 62.67, 62.65, 62.2.



trans-**4a** i-**4a**

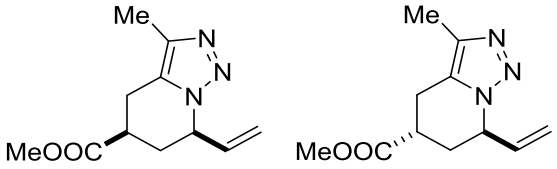
Methyl (*E*)-6-azidohex-4-enoate (*trans*-4a) methyl 4-azidohex-5-enoate (i-4a). Following the general procedure for **3a**, methyl 4-pentenoate (2.0 g, 17.50 mmol), allyl bromide (6.35 g, 52.5 mmol), HG-2 (0.22 g, 0.35 mmol), and NaN_3 (4.55 g, 70 mmol) afforded *trans*-**4a** and i-**4a** (62:38 ratio, 1.05 g, 39%) as a colorless oil. *trans*-**4a** and i-**4a**: R_f = 0.3 (10% EtOAc/hexanes); IR (neat) 2098, 1738 cm^{-1}. *trans*-**4a**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 – 5.64 (m, 1H), 5.64 – 5.48 (m, 1H), 3.87 – 3.69 (m, 2H), 3.68 (s, 3H), 2.56 – 2.32 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.31, 134.60, 124.37, 52.71, 51.79, 33.65, 27.57. i-**4a** (diagnostic peaks only): ^1H NMR (400 MHz, $CDCl_3$) δ 5.38 – 5.25 (m, 2H), 3.92 (q, *J* = 7.3 Hz, 1H), 3.88 – 3.82 (m, 1H), 1.94 – 1.78 (m, 2H).



trans-**21** i-**21**

Methyl (*E*)-6-azido-2-(but-2-yn-1-yl)hex-4-enoate (*trans*-21) methyl 4-azido-2-(but-2-yn-1-yl)hex-5-enoate (i-21). To a solution of diisopropylamine (0.25 g, 2.51 mmol) in anhydrous THF (6 mL) under N_2 atmosphere at 0 °C was slowly added *n*-BuLi (0.9 mL, 2.5 M in hexane, 2.32 mmol). The ice bath was removed after 10 min and the reaction stirred for another 20 min. In another flask *trans*-**4a** and i-**4a** (0.3 g, 1.92 mmol) were dissolved in THF (10 mL) at -78 °C and to this prepared LDA was slowly added at -78 °C. The reaction mixture was stirred for 30 min and then propargyl bromide (80 wt% in toluene, 0.44 g, 3.28 mmol) was added. The resulting mixture was stirred for 1 h at -78 °C. NH_4Cl and H_2O were added. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organics washed with water (1 × 20 mL) and brine, and dried over Na_2SO_4. Filtration and concentration gave a residue, which was purified by automated chromatography (silica, hexane/EtOAc 9:1) to give mixture of *trans*-**21**, and i-**21** (0.11 g, 26%,

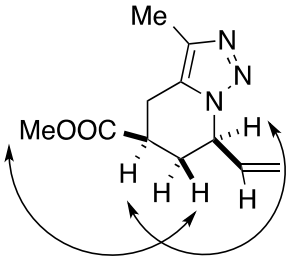
71:29) as a colorless oil. *trans*-**21** and i-**21**: R_f = 0.3 (10% EtOAc/hexanes); IR (neat) 2098, 1736 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{11}H_{16}N_3O$ $[M + H]^+$ 222.1243, found 222.1233. *trans*-**21**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 – 5.50 (m, 2H), 3.77 – 3.62 (m, 5H), 2.69 – 2.55 (m, 1H), 2.54 – 2.31 (m, 4H), 1.77 (t, *J* = 2.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 132.6, 126.0, 77.8, 75.7, 52.7, 52.0, 44.6, 33.7, 21.1, 3.6. i-**21** (diagnostic peaks only): ^1H NMR (400 MHz, $CDCl_3$) δ 5.37 – 5.24 (m, 2H), 3.97 – 3.90 (m, 1H), 3.89 – 3.84 (m, 1H), 2.77 – 2.67 (m, 1H), 2.02 – 1.89 (m, 1H).



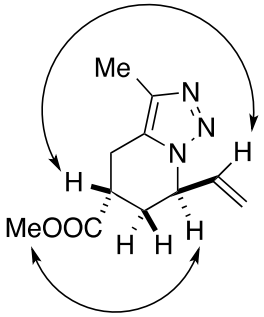
25a **25b**

Methyl (5*R,7*R**)-3-methyl-7-vinyl-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyridine-5-carboxylate (25a), methyl (5*S**,7*R**)-3-methyl-7-vinyl-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyridine-5-carboxylate (25b).** Azides *trans*-**21** and i-**21** (0.10 g, 0.45 mmol) were dissolved in toluene (10 mL). The reaction mixture was heated at reflux for 24 h. The solvent was evaporated after cooling the reaction mixture to room temperature. The residue was purified by automated chromatography (silica, hexane:EtOAc/9:1) to give 0.080 g (80%) of the title products (anti:syn 1:1.5) as a colorless yellow solid. R_f = 0.3 (50% EtOAc/hexanes); IR (neat) 1734 cm^{-1}; HRMS (ESI) m/z calculated for $(C_{11}H_{15}N_3O+H)^+$ 222.1243, found: 222.1286. **25a:** ^1H NMR (500 MHz, $CDCl_3$) δ 6.05 (ddd, *J* = 17.4, 10.2, 7.5 Hz, 1H), 5.53 – 5.38 (m, 2H), 4.90 – 4.77 (m, 1H), 3.77 (s, 3H), 3.16 – 3.07 (m, 1H), 2.93 – 2.77 (m, 2H), 2.59 – 2.49 (m, 1H), 2.27 (d, *J* = 2.9 Hz, 3H), 2.00 (dt, *J* = 13.7, 11.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 139.4, 135.3, 128.8, 119.5, 59.9, 52.6, 37.6, 33.1, 22.9, 10.1. **25b**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.96 (ddd, *J* = 17.1, 10.6, 4.9 Hz,

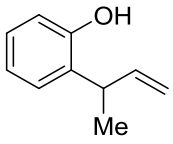
1H), 5.30 (d, *J* = 9.8 Hz, 2H), 4.90 – 4.83 (m, 1H), 3.76 (s, 3H), 3.07 (dd, *J* = 16.2, 5.5 Hz, 1H), 3.03 – 2.95 (m, 1H), 2.87 (dd, *J* = 16.0, 9.9 Hz, 1H), 2.37 (d, *J* = 13.8 Hz, 1H), 2.27 (d, *J* = 2.7 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 139.2, 136.0, 128.5, 118.1, 56.9, 52.6, 33.8, 30.8, 22.5, 10.1. The following NOE correlations were used to assign **25a** and **25b**:



25a



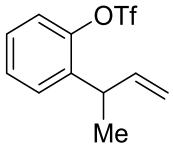
25b



5a

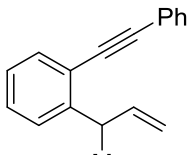
2-(But-3-en-2-yl)phenol (5a).[49] Following the general procedure for **2a,** phenol (10 g, 106 mmol), crotyl chloride (14.43 g, 159.3 mmol), and NaH (3.8 g, 159.3 mmol) afforded (*E*)-(but-2-en-1-yloxy)benzene (8.3 g), which was used as obtained in the next reaction. The crude obtain was dissolved in DMF (5 mL) and irradiated in microwave for 20 min at 250 °C. The reaction mixture was cooled and H_2O was added. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organics washed with water (1 × 20 mL) and brine, and dried over Na_2SO_4. Filtration and concentration gave a residue, which was purified by automated chromatography (silica, hexane/EtOAc 9.5:0.5) to give 2-(but-3-en-2-yl)phenol (**5a**, 5.2 g, 33%) as a colorless oil. R_f = 0.30 (10% EtOAc/hexanes); IR (neat) 3466 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.22 – 7.08 (m, 2H), 6.93 (td, *J* = 7.5, 1.3 Hz, 1H), 6.89 – 6.72 (m, 1H), 6.10 (ddd, *J* = 17.3, 10.3, 5.9 Hz, 1H),

5.24 – 5.19 (m, 1H), 5.19 – 5.16 (m, 1H), 5.12 (s, 1H), 3.72 (ddt, *J* = 7.4, 5.9, 1.6 Hz, 1H), 1.41 (d, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 142.5, 130.5, 128.1, 127.7, 121.1, 116.3, 114.5, 37.8, 18.9.



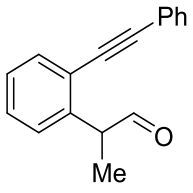
6a

2-(But-3-en-2-yl)phenyl trifluoromethanesulfonate (6a). 2-(But-3-en-2-yl)phenol (**5a**, 0.74 g, 4.99 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. Pyridine (0.79 g, 9.98 mmol) was added to it at 0 °C and Tf_2O (1.69 g, 5.99 mmol) was added over 20 min. The reaction mixture was stirred for 10 min at 0 °C and quenched by aq HCl. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics washed with water (1 × 20 mL) and brine, and dried over Na_2SO_4. Filtration and concentration gave a residue, which was purified by automated chromatography (silica, hexane) to give **6a** (1.0 g, 71%) of as a colorless oil. R_f = 0.8 (10% EtOAc/hexanes); IR (neat) 1213 cm^{-1}; HRMS (ESI) m/z calculated for $(C_{11}H_{11}F_3O_3S\text{-}H)^+$ 279.0303, found: 279.0301. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.32 – 7.26 (m, 2H), 5.96 (ddd, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.18 – 5.04 (m, 2H), 3.87 (qdt, *J* = 7.1, 5.8, 1.6 Hz, 1H), 1.37 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 141.0, 138.3, 129.3, 128.7, 128.0, 121.4, 118.7 (*J* = 319.7), 114.7, 36.0, 20.1.



7a

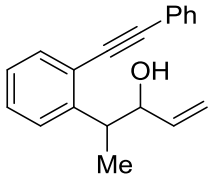
1-(But-3-en-2-yl)-2-(phenylethynyl)benzene (7a).[50] 2-(But-3-en-2-yl)phenyl trifluoromethanesulfonate (**6a**, 1.51 g, 5.41 mmol) was dissolved in DMSO (10 mL) under N_2 atmosphere. Ethynylbenzene (0.83 g, 8.12 mmol), $Pd(OAc)_2$ (0.04 g, 0.16 mmol), PPh_3 (0.17 g, 0.65 mmol), and K_3PO_4 (2.29 g, 6.49 mmol) were added and resulting reaction mixture was heated at 80 °C for 24 h. The reaction was quenched by H_2O. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organics washed with water (1 × 20 mL) and brine, and dried over Na_2SO_4. Filtration and concentration gave a residue, which was purified by automated chromatography (silica, hexane) to give **7a** (1.0 g, 80%) of as a colorless oil. R_f = 0.8 (hexane); IR (neat) 1637 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.48 (m, 3H), 7.47 – 7.13 (m, 6H), 6.11 (ddd, *J* = 17.3, 10.3, 5.9 Hz, 1H), 5.26 – 5.05 (m, 2H), 4.18 (ttd, *J* = 7.1, 5.5, 1.7 Hz, 1H), 1.44 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5, 142.4, 132.5, 131.6, 128.8, 128.5, 128.4, 126.5, 126.1, 123.6, 122.4, 113.6, 93.4, 88.2, 40.6, 19.9.



8a

2-(2-(Phenylethynyl)phenyl)propanal (8a). 1-(But-3-en-2-yl)-2-(phenylethynyl)benzene (**7a**, 1.58 g, 6.77 mmol) was dissolved in anhydrous CH_2Cl_2 (100 mL) under an N_2 atmosphere. The solution was cooled to -78 °C, and a stream of O_3/O_2 was introduced through a disposable pipet for a period of 20 min. The reaction was then purged with O_2 followed by N_2. The reaction was quenched with dimethylsulfide (2.1 g, 3.38 mmol). H_2O was added to the reaction mixture. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers washed with water (1 × 20 mL) and brine, and dried over Na_2SO_4. Filtration and concentration

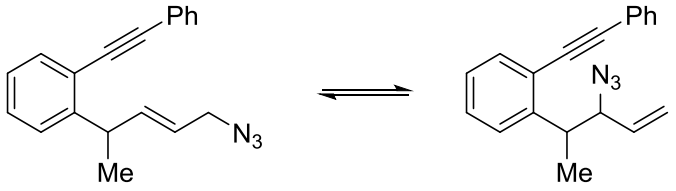
gave a residue, which was purified by automated chromatography (silica, hexane:EtOAc/9:1) to give **8a** (0.46 g, 29%) of as a colorless oil. R_f = 0.6 (10% EtOAc/hexanes); IR (neat) 1637 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{13}O$ $[M - H]^-$ 233.0967, found 233.0951. ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.64 – 7.60 (m, 1H), 7.56 – 7.50 (m, 2H), 7.40 – 7.34 (m, 4H), 7.31 (td, *J* = 7.5, 1.5 Hz, 1H), 7.18 (dd, *J* = 7.6, 1.4 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 1H), 1.51 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3, 140.2, 133.0, 131.6, 129.2, 128.8, 128.6, 128.1, 127.6, 123.6, 122.9, 94.3, 87.4, 51.4, 14.3.



9a

4-(2-(Phenylethynyl)phenyl)pent-1-en-3-ol (9a). To a stirred solution of vinylmagnesium bromide (0.74 g, 5.63 mmol) in anhydrous THF (30 mL) at -78 °C under N_2 atmosphere was slowly added a solution of 2-(2-(phenylethynyl)phenyl)propanal (**8a**, 0.05 g, 0.21 mmol) in anhydrous THF (5 mL). The reaction mixture was stirred for 2 h at -78 °C and then brought to room temperature. The reaction was quenched with aq NH_4Cl solution. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers washed with water (1 × 20 mL) and brine, and dried over Na_2SO_4. Filtration and concentration gave a residue, which was purified by automated chromatography (silica, hexane:EtOAc/9:1) to give **9a** (0.02 g, 29%) of as a colorless oil. R_f = 0.4 (10% EtOAc/hexanes); IR (neat) 3415 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}NO$ $C_{13}H_{17}O_3$ $[M + NH_4]^+$ 280.1702, found 280.1725. ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.46 (m, 3H), 7.44 – 7.29 (m, 5H), 7.22 (ddd, *J* = 7.6, 5.2, 3.4 Hz, 1H), 5.94 (ddd, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.30 – 5.05 (m, 2H), 4.45 (q, *J* = 4.9 Hz, 1H), 3.70 – 3.56 (m, 1H), 1.36 (d, *J* = 7.1 Hz, 2H);

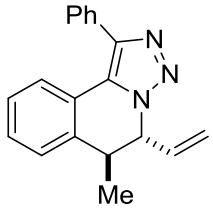
^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7, 139.6, 132.6, 131.6, 128.6, 128.5, 128.5, 127.2, 126.4, 123.4, 122.9, 115.4, 93.8, 88.2, 76.4, 42.8, 14.2.



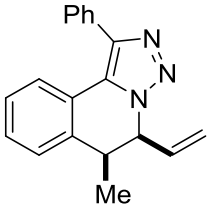
trans-**22** i-**22**

(*E*)-1-(5-Azidopent-3-en-2-yl)-2-(phenylethynyl)benzene (*trans*-22), 1-(3-azidopent-4-en-2-yl)-2-(phenylethynyl)benzene (i-**22).** Triethylamine was added to a solution of 4-(2-(phenylethynyl)phenyl)pent-1-en-3-ol (**9a**, 0.05 g, 0.20 mmol) and methanesulfonyl chloride (0.04 g, 0.30 mmol) in CH_2Cl_2 (5 mL) under N_2 atmosphere at 0 °C. The reaction mixture was stirred at room temperature for 2 h. H_2O was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (1 × 20 mL) and brine, and dried over Na_2SO_4. Filtration and concentration gave a residue. A suspension of the residue and sodium azide (0.04 g, 0.61 mmol) in DMF (10 mL) was stirred for 3 h at room temperature. Saturated solution of aq NH_4Cl was added. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with water (1 × 20 mL) and brine, and dried over Na_2SO_4. Filtration and concentration gave a residue, which was purified by automated chromatography (silica, hexane/EtOAc 9.5:0.5) to give mixture of *trans*-**22**, and i-**22** (0.03 g, 52%, 85:15) as a colorless oil. *trans*-**22** and i-**22**: R_f = 0.7 (10% EtOAc/hexanes); IR (neat) 2097 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_3$ $[M + H]^+$: 288.1501, found: 288.1513. *trans*-**22**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.48 (m, 3H), 7.40 – 7.28 (m, 4H), 7.25 – 7.18 (m, 1H), 6.01 (ddt, *J* = 15.3, 6.1, 1.2 Hz, 1H), 5.63 (dtd, *J* = 15.2, 6.6, 1.6 Hz, 1H), 4.20 (p, *J* = 6.9 Hz, 1H), 3.76 (dt, *J* = 6.6, 1.2 Hz, 2H), 1.45 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8, 140.4, 132.6, 131.6,

128.9, 128.6, 128.5, 126.5, 126.3, 123.5, 122.4, 122.3, 93.7, 88.0, 52.9, 39.6, 20.4. i-**22** (diagnostic peaks only): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 – 5.69 (m, 1H), 5.37 – 5.15 (m, 2H), 4.29 (t, *J* = 7.6 Hz, 1H), 3.62 (dt, *J* = 13.3, 6.9 Hz, 1H).

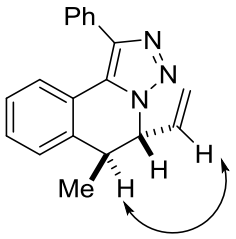


26a

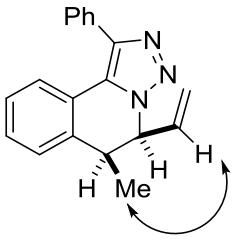


26b

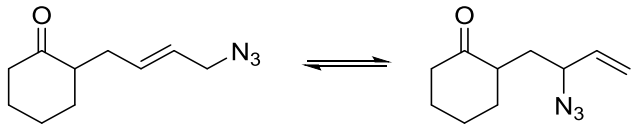
(5*S,6*R**)-6-Methyl-1-phenyl-5-vinyl-5,6-dihydro-[1,2,3]triazolo[5,1-*a*]isoquinoline (26a) and (5*S**,6*S**)-6-methyl-1-phenyl-5-vinyl-5,6-dihydro-[1,2,3]triazolo[5,1-*a*]isoquinoline (26b).** Azides *trans*-**22** and i-**22** (0.03 g) were dissolved in toluene (10 mL). The reaction mixture was heated at reflux for 12 h. The solvent was evaporated after cooling the reaction mixture to room temperature. The residue was purified by automated chromatography (silica, hexane:EtOAc/8:2) to give **26a** and **26b** (0.02 g, 80%) (**26a**:**26b**/1.4:1) as a colorless solid. **26a** and **26b:** R_f = 0.3 (20% EtOAc/hexanes); IR (neat) 2926 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_3$ $[M + H]^+$ 288.1501, found 288.1473. **26a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 – 7.71 (m, 3H), 7.51 – 7.40 (m, 4H), 7.37 – 7.29 (m, 2H), 5.81 (ddd, *J* = 17.1, 10.4, 5.8 Hz, 1H), 5.25 – 5.20 (m, 1H), 5.13 (dt, *J* = 10.6, 0.8 Hz, 1H), 5.00 – 4.89 (m, 1H), 3.30 (qd, *J* = 7.2, 2.3 Hz, 1H), 1.32 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.2, 137.2, 134.8, 131.9, 129.6, 128.8, 128.7, 128.6, 127.9, 127.6, 126.6, 124.7, 123.6, 118.2, 63.8, 40.4, 20.8. **26b** (diagnostic peaks only): ^{1}H NMR (500 MHz, $CDCl_3$) δ5.89 – 5.83 (m, 1H), 5.34 – 5.26 (m, 2H), 5.23 (dq, *J* = 5.7, 2.0 Hz, 2H), 3.52 (qd, *J* = 7.0, 4.9 Hz, 1H), 1.43 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.3, 136.8, 131.8, 131.0, 127.5, 124.5, 120.8, 63.4, 38.1, 14.4. The following NOE correlations were used to assign **26a** and **26b**:



26a

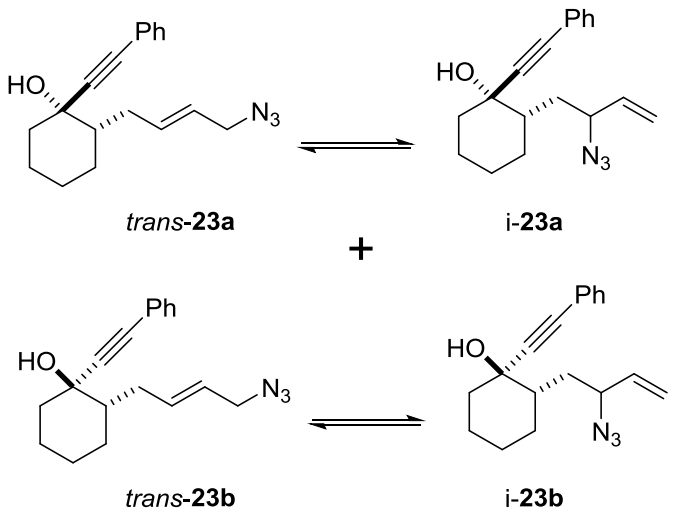


26b



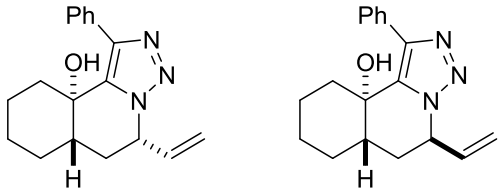
trans-**10a** i-**10a**

(*E*)-2-(4-Azidobut-2-en-1-yl)cyclohexan-1-one (*trans*-10a), 2-(2-azidobut-3-en-1-yl)cyclohexan-1-one (i-10a). Following the general procedure for **3a**, 2-allylyclohexanone (2.0 g, 14.40 mmol), allyl bromide (5.25 g, 43.4 mmol), HG-2 (0.18 g, 0.28 mmol), and NaN_3 (3.74 g, 57.60 mmol) afforded azides ***trans*-10a** and **i-10a** (81:19 ratio, 1.53 g, 55%) as a colorless oil. *trans*-**10a** and i-**10a**: R_f = 0.3 (10% EtOAc/hexanes); IR (neat) 2096, 1709 cm^{-1}. *trans*-**10a**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 – 5.65 (m, 1H), 5.61 – 5.46 (m, 1H), 3.68 (d, *J* = 6.6 Hz, 2H), 2.53 (dtd, *J* = 14.4, 5.8, 1.3 Hz, 1H), 2.46 – 2.22 (m, 3H), 2.19 – 1.93 (m, 3H), 1.86 (dtd, *J* = 9.3, 3.5, 1.9 Hz, 1H), 1.75 – 1.54 (m, 2H), 1.46 – 1.27 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.2, 134.6, 124.8, 52.8, 50.4, 42.2, 33.6, 32.3, 28.0, 25.1. i-**10a** (diagnostic peaks only): ^1H NMR (400 MHz, $CDCl_3$) δ 5.34 – 5.15 (m, 2H), 4.05 – 3.91 (m, 1H), 3.91 – 3.78 (m, 1H).



(1*R,2*R**)-2-((*E*)-4-Azidobut-2-en-1-yl)-1-(phenylethynyl)cyclohexan-1-ol (*trans*-23a), (1*R**,2*R**)-2-(2-azidobut-3-en-1-yl)-1-(phenylethynyl)cyclohexan-1-ol (i-23a), (1*R**,2*S**)-2-((*E*)-4-azidobut-2-en-1-yl)-1-(phenylethynyl)cyclohexan-1-ol (*trans*-23b), (1*R**,2*S**)-2-(2-azidobut-3-en-1-yl)-1-(phenylethynyl)cyclohexan-1-ol (i-23b).** Azides *trans*-**10a** and i-**10** (0.3 g, 1.55 mmol) were dissolved in THF (10 mL) at -78 °C and stirred for 30 min. Then lithium phenylacetylide (1M in THF, 0.17 g, 1.55 mmol) was added to the reaction mixture and stirred for 2 h at -78 °C. The reaction was brought to room temperature and stirred for 2 h. NH_4Cl and H_2O were added. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organics washed with water (1 × 20 mL) and brine, and dried over Na_2SO_4. Filtration and concentration gave a residue, which was purified by automated chromatography (silica, hexane/EtOAc 9:1) to give mixture of azides *trans*-**23a**, i-**23a** (0.12 g, 25%), and *trans*-**23b,** and i-**23b** (0.12 g, 26%) (**23a:23b**/1:1) of as a colorless oil. *trans*-**23a** and i-**23a** (81:19) : R_f = 0.3 (20% EtOAc/hexanes); IR (neat) 2100 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{22}N_3O$ $[M + H]^+$ 296.1763, found 296.1768. *trans*-**23a**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.36 (m, 2H), 7.31 (ddd, *J* = 3.8, 2.6, 1.5 Hz, 3H), 5.93 – 5.70 (m, 1H), 5.66 – 5.50 (m, 1H), 3.93 – 3.83 (m, 1H), 3.78 – 3.66 (m, 1H), 2.84 – 2.63 (m, 1H), 2.30 – 1.95 (m, 2H), 1.89 – 1.58 (m, 6H), 1.44 – 1.19 (m, 2H); ^{13}C NMR (101 MHz,

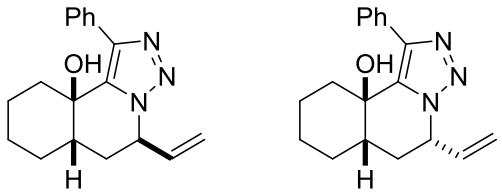
$CDCl_3$) δ 135.9, 131.8, 128.4, 128.4, 124.6, 122.9, 93.6, 84.0, 70.3, 53.0, 46.0, 40.0, 34.0, 26.1, 25.0, 21.3. i-**23a** (diagnostic peaks only): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53 – 5.37 (m, 1H), 5.36 – 5.21 (m, 3H), 4.02 (q, *J* = 7.7 Hz, 1H), 3.94 (ddd, *J* = 11.1, 7.3, 4.2 Hz, 1H), 3.87 (d, *J* = 7.3 Hz, 3H). *trans*-**23b** and i-**23b** (mixture; 83:17): R_f = 0.25 (20% EtOAc/hexanes); IR (neat) 2099 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{22}N_3O$ $[M + H]^+$ 296.1763, found 296.1771. *trans*-**23b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.38 (m, 2H), 7.37 – 7.29 (m, 3H), 5.92 – 5.72 (m, 1H), 5.69 – 5.51 (m, 1H), 3.73 (d, J = 6.6 Hz, 2H), 2.75 (dddd, J = 14.2, 6.8, 4.2, 1.4 Hz, 1H), 2.21 (s, 1H), 2.17 – 1.98 (m, 2H), 1.90 – 1.58 (m, 5H), 1.35 – 1.13 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0, 131.8, 128.5, 128.5, 124.7, 122.9, 90.1, 86.9, 73.3, 53.0, 48.0, 41.5, 34.2, 29.5, 25.6, 24.3. i-**23b** (diagnostic peaks only): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 – 5.24 (m, 3H), 4.09 (q, *J* = 7.5 Hz, 1H), 4.05 – 3.94 (m, 1H).



27a **27b**

(5***R***,6a***R***,10a***R***)-1-Phenyl-5-vinyl-6,6a,7,8,9,10-hexahydro-[1,2,3]triazolo[5,1-*a*]isoquinolin-10a(5*H*)-ol (27a), (5***S***,6a***R***,10a***R***)-1-phenyl-5-vinyl-6,6a,7,8,9,10-hexahydro-[1,2,3]triazolo[5,1-*a*]isoquinolin-10a(5*H*)-ol (27b).** Azides *trans*-**23a** and i-**23a** (0.09 g, 0.30 mmol) were dissolved in toluene (10 mL) and heated at reflux for 15 h. The solvent was evaporated after cooling the reaction mixture to room temperature. The residue was purified by automated chromatography (silica, hexane:EtOAc/8:2) to give **27a** (0.06 g, 65%) and **27b** (0.03 g, 32%) (**27a**:**27b** 2.9:1) as a colorless solid. **27a**: R_f = 0.3 (50% EtOAc/hexanes); mp 227-229 °C; IR (neat) 981 cm^{-1}; HRMS (ESI) m/z calculated for $(C_{18}H_{21}N_3O+H)^+$ 296.1763, found: 296.1743. ^{1}H NMR

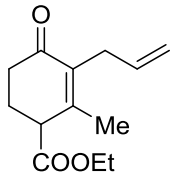
(500 MHz, $CDCl_3$) δ 7.70 – 7.61 (m, 2H), 7.49 – 7.32 (m, 3H), 6.13 (ddd, *J* = 17.4, 10.2, 7.6 Hz, 1H), 5.48 (dt, *J* = 17.2, 1.0 Hz, 1H), 5.40 (dt, *J* = 10.1, 0.9 Hz, 1H), 4.97 – 4.88 (m, 1H), 2.27 (dd, *J* = 13.9, 3.5 Hz, 1H), 1.99 (s, 1H), 1.85 (ddd, *J* = 13.9, 5.5, 2.3 Hz, 1H), 1.78 (dddd, *J* = 12.8, 10.8, 4.3, 2.3 Hz, 2H), 1.70 – 1.45 (m, 4H), 1.38 – 1.14 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.5, 136.4, 135.3, 132.5, 129.8, 128.4, 128.3, 118.7, 67.0, 61.9, 42.0, 34.3, 32.2, 26.7, 25.5, 20.8. **27b**: R_f = 0.25 (50% EtOAc/hexane); mp 155-157 °C; HRMS (ESI) *m/z* calcd for $C_{18}H_{22}N_3O$ $[M + H]^+$ 296.1763, found 296.1776; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.63 (m, 2H), 7.55 – 7.33 (m, 3H), 6.04 (ddd, *J* = 17.1, 10.3, 5.2 Hz, 1H), 5.39 – 5.25 (m, 2H), 4.95 (dd, *J* = 17.1, 1.5 Hz, 1H), 2.51 – 2.39 (m, 1H), 2.32 (dt, *J* = 13.8, 3.5 Hz, 1H), 1.94 – 1.85 (m, 1H), 1.83 – 1.73 (m, 1H), 1.74 – 1.42 (m, 4H), 1.39 – 1.17 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.2, 136.7, 135.3, 132.4, 129.7, 128.4, 128.3, 117.5, 67.1, 58.6, 37.7, 34.0, 29.9, 26.6, 25.5, 20.8.



28a **28b**

(5*R,6a*S**,10a*R**)-1-Phenyl-5-vinyl-6,6a,7,8,9,10-hexahydro-[1,2,3]triazolo[5,1-*a*]isoquinolin-10a(5*H*)-ol (28a), (5*S**,6a*S**,10a*R**)-1-phenyl-5-vinyl-6,6a,7,8,9,10-hexahydro-[1,2,3]triazolo[5,1-*a*]isoquinolin-10a(5*H*)-ol (28b).** Azides *trans*-**23b** and i-**23b** (0.12 g, 0.40 mmol) was dissolved in toluene (10 mL) and heated at reflux for 8 h. The solvent was evaporated after cooling the reaction mixture to room temperature. The residue was purified by automated chromatography (silica, hexane:EtOAc/8:2) to give **28a** and **28b** (0.11 g, 96%) (28a:28b 6.2:1) as a colorless solid. **28a** and **28b**: R_f = 0.3 (50% EtOAc/hexanes); mp 182-184 °C; IR (neat) 2900 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{22}N_3O$ $[M + H]^+$ 296.1763, found 296.1789. **28a**: ^1H NMR

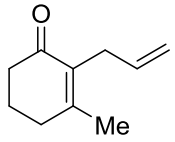
(500 MHz, $CDCl_3$) δ 7.78 – 7.69 (m, 2H), 7.41 (tdd, *J* = 8.7, 6.6, 5.1 Hz, 3H), 6.09 (ddd, *J* = 16.9, 10.3, 6.5 Hz, 1H), 5.37 (dt, *J* = 10.5, 0.9 Hz, 1H), 5.33 – 5.21 (m, 1H), 5.12 (d, *J* = 7.0 Hz, 1H), 2.37 (s, 1H), 2.23 – 2.06 (m, 2H), 1.96 – 1.80 (m, 1H), 1.79 – 1.44 (m, 4H), 1.41 – 1.19 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.8, 136.7, 136.2, 132.3, 129.6, 128.4, 128.4, 118.3, 69.6, 57.5, 35.4, 31.7, 31.0, 27.3, 22.8, 22.8, 14.3. **28b** (diagnostic peaks only): ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.80 (m, 2H), 6.15 (dd, *J* = 10.1, 7.4 Hz, 1H), 5.52 – 5.45 (m, 1H), 5.42 (d, *J* = 10.3 Hz, 1H), 4.90 (dt, *J* = 10.6, 6.1 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.4, 128.5, 128.3, 119.0, 69.9, 61.1, 34.8, 34.2, 33.9, 26.7, 21.4, 14.4.



11aa

Ethyl 3-Allyl-2-methyl-4-oxocyclohex-2-ene-1-carboxylate (11aa). Hagemann's ester (10 g, 54.80 mmol) was rapidly added to a stirred solution of potassium *tert*-butoxide (6.77 g, 60.30 mmol) in dry *tert*-butanol (30 mL). The red solution so formed turned into a straw-yellow suspension few minutes later after the addition. The reaction mixture was stirred for 15 min and then ally bromide (7.29 g, 5.22 mmol) was added in a single portion. The mixture was allowed to reflux for 12 h. The reaction mixture was allowed to cool to room temperature and then aq HCl and CH_2Cl_2 were added. the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics washed with water (1 × 20 mL) and brine, and dried over Na_2SO_4. Filtration and concentration gave a residue, which was purified by automated chromatography (silica, hexane/EtOAc 9.5:0.5) to give **11aa** (7.7 g, 63%) as a colorless oil. R_f = 0.6 (10% EtOAc/hexanes); IR (neat) 1729, 1669 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{19}O_3$ $[M + H]^+$: 223.1334, found:

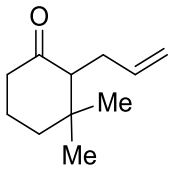
223.1356. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (ddt, *J* = 16.5, 10.5, 5.9 Hz, 1H), 5.05 – 4.89 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.31 (t, *J* = 5.0 Hz, 1H), 3.10 (ddt, *J* = 5.6, 3.5, 1.7 Hz, 2H), 2.59 (ddd, *J* = 16.9, 11.7, 5.2 Hz, 1H), 2.45 – 2.35 (m, 1H), 2.35 – 2.15 (m, 2H), 1.97 (d, *J* = 0.7 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.1, 172.3, 151.7, 135.1, 135.0, 114.8, 61.4, 47.9, 34.7, 29.3, 25.8, 20.6, 14.3.



12aa

2-Allyl-3-methylcyclohex-2-en-1-one (12aa). The compound **12aa** was prepared following the procedure reported by Aubé et al.[40] The starting ester (**11aa**, 7.68 g, 34.50 mmol) was dissolved in 1/1 mixture of ethanol and water (40 mL) and $LiOH{\cdot}H_2O$ (2.90 g, 6.91 mmol) was added as a powder. The mixture was stirred 3 h, concentrated, and the residue partitioned between water and Et_2O. The aqueous phase was acidified with 6 M aq HCl and extracted with CH_2Cl_2. The organic extracts combined, dried over Na_2SO_4, and concentrated. The residue was dissolved in a mixture of concentrated HCl (3 mL) in THF (50 mL) and heated for 24 h at 90 °C. The reaction mixture was allowed to cool to room temperature and then aq HCl and CH_2Cl_2 were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics washed with water (1 × 20 mL) and brine, and dried over Na_2SO_4. Filtration and concentration gave a residue, which was purified by automated chromatography (silica, hexane/EtOAc 9:1) to give **12aa** (3.86 g, 74%) as dark yellow oil. R_f = 0.5 (20% EtOAc/hexanes); IR (neat) 1662 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{10}H_{15}O$ $[M + H]^+$ 151.1123, found 151.1145. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (ddt, *J* = 17.7, 9.4, 6.1 Hz, 1H), 5.01 – 4.87 (m, 2H), 3.06 (dt, *J* = 6.2, 1.5 Hz, 2H), 2.42 – 2.34 (m, 4H), 2.02 –

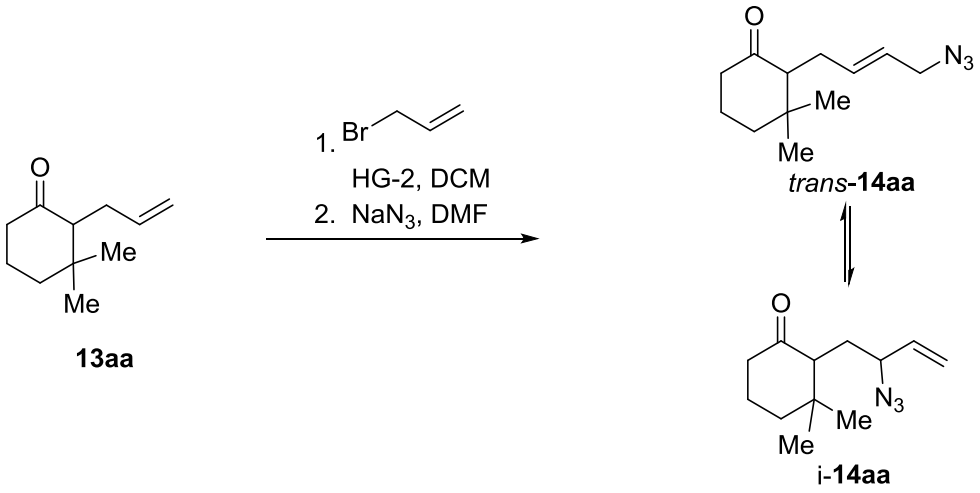
1.94 (m, 2H), 1.93 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 157.0, 135.9, 133.2, 114.4, 37.8, 33.1, 29.4, 22.4, 21.3.



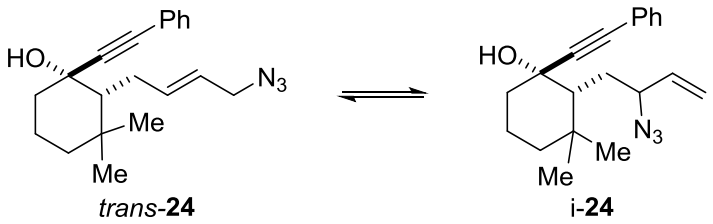
13aa

2-Allyl-3,3-dimethylcyclohexan-1-one (13aa). Compound **13aa** prepared following the procedure reported by Reetz and Kindler.[51] Lithium chloride (0.11 g, 2.66 mmol) and CuI (0.25 g, 1.33 mmol) were dissolved in anhydrous THF (90 mL) under argon at room temperature. The resulting solution was cooled to -40 °C (dry ice/acetonitrile), ketone **12aa** (2.0 g, 13.30 mmol) and TMSCl (1.59 g, 14.60 mmol) were added, and the solution was stirred for 10 min. MeMgCl (3 M in THF, 1.49 g, 19.90 mmol) was added dropwise and left stirring at -40 °C for 1.5 h. The reaction mixture was then poured into saturated aq NH_4Cl (150 mL) and Et_2O (150 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organics washed with water (1 × 20 mL) and brine, and dried over Na_2SO_4. Filtration and concentration gave a residue, which was dissolved in THF (40 mL) and stirred with TBAF (1 M in THF, 20 mL, 19.9 mmol) at room temperature for 30 min under N_2 atmosphere. The mixture was poured into H_2O and Et_2O, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organics washed with water (1 × 20 mL) and brine, and dried over Na_2SO_4. Filtration and concentration gave a residue, which was purified by automated chromatography (silica, hexane/EtOAc 9:1) to give **13aa** (1.67 g, 76%) as a colorless oil. R_f = 0.5 (10% EtOAc/hexanes); IR (neat) 1709 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (dddd, J = 17.2, 10.1, 7.2, 6.4 Hz, 1H), 5.11 – 4.77 (m, 2H), 2.45 (dddt, J = 14.1, 10.3, 6.4, 1.3 Hz, 1H), 2.39 – 2.18 (m, 3H), 2.06 (dddt, J = 14.2, 7.3, 2.9, 1.4 Hz, 1H), 1.97 – 1.72 (m, 2H), 1.70 – 1.54

(m, 2H), 1.07 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.8, 138.0, 115.3, 61.1, 41.4, 39.8, 39.3, 29.6, 28.8, 23.2, 22.2.

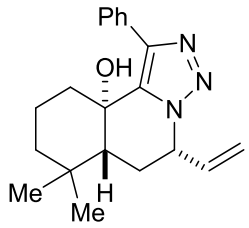


(*E*)-2-(4-Azidobut-2-en-1-yl)-3,3-dimethylcyclohexan-1-one (*trans*-14aa), 2-(2-azidobut-3-en-1-yl)-3,3-dimethylcyclohexan-1-one (i-14aa). Following the general procedure for **3a**, 2-allyl-3,3-dimethylcyclohexan-1-one (**13aa,** 1.66 g, 9.95 mmol), allyl bromide (3.61 g, 29.80 mmol), HG-2 (0.12 g, 0.20 mmol), and NaN_3 (2.59 g, 39.80 mmol) afforded azides *trans*-**14aa** and i-**14aa** (72:28 ratio, 1.32 g, 60%) as a colorless oil. Azides *trans*-**14aa** and i-**14aa**: R_f = 0.4 (10% EtOAc/hexanes); IR (neat) 2095, 1708 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{23}N_4O$ $[M + H]^+$ 239.1872, found 239.1869. *trans*-**14aa**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (dddt, *J* = 15.1, 7.5, 6.3, 1.2 Hz, 1H), 5.51 (dtt, *J* = 15.0, 6.7, 1.3 Hz, 1H), 3.71 – 3.57 (m, 2H), 2.54 – 2.41 (m, 1H), 2.40 – 2.18 (m, 3H), 2.07 (dddd, *J* = 14.1, 7.7, 2.6, 1.2 Hz, 1H), 2.01 – 1.75 (m, 2H), 1.74 – 1.52 (m, 2H), 1.08 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.3, 136.3, 123.9, 61.4, 52.8, 41.6, 40.0, 39.8, 29.7, 27.0, 23.2, 21.7. i-**14aa** (diagnostic peaks only): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 – 5.12 (m, 2H), 3.88 – 3.77 (m, 1H), 1.42 – 1.27 (m, 1H).

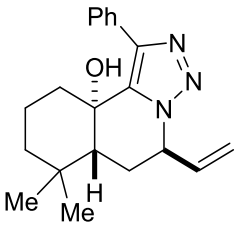


trans-**24** i-**24**

(1*R,2*S**)-2-((*E*)-4-Azidobut-2-en-1-yl)-3,3-dimethyl-1-(phenylethynyl)cyclohexan-1-ol (*trans*-24), (1*R**,2*S**)-2-(2-azidobut-3-en-1-yl)-3,3-dimethyl-1-(phenylethynyl)cyclohexan-1-ol (i-24).** Azides *trans*-**14aa** and i-**14aa** (1.31 g, 5.93 mmol) were dissolved in THF (20 mL) at -78 °C and stirred for 30 min. Then lithium phenylacetylide (1M in THF, 5.93 mL, 5.93 mmol) was added to the reaction mixture and stirred for 2 h at -78 °C. The reaction was brought to room temperature and stirred for 2 h. NH_4Cl and H_2O were added. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organics washed with water (1 × 20 mL) and brine, and dried over Na_2SO_4. Filtration and concentration gave a residue, which was purified by automated chromatography (silica, hexane/EtOAc 9:1) to give mixture of azides *trans*-**24**, and i-**24** (1.12 g, 58%) as a colorless oil. *trans*-**24** and i-**24** (mixture; 68:32) : R_f = 0.4 (10% EtOAc/hexanes); IR (neat) 3256, 2100 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{26}N_3O$ $[M + H]^+$: 324.2076, found: 324.2051. *trans*-**24**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 2H), 7.30 (dp, *J* = 5.3, 1.7 Hz, 3H), 6.13 – 5.97 (m, 1H), 5.65 – 5.52 (m, 1H), 3.66 (d, *J* = 5.7 Hz, 2H), 2.75 – 2.59 (m, 1H), 2.42 – 2.32 (m, 1H), 2.16 – 2.03 (m, 1H), 1.81 (dddd, *J* = 10.0, 5.1, 2.8, 1.3 Hz, 2H), 1.71 (d, *J* = 3.1 Hz, 1H), 1.55 – 1.41 (m, 2H), 1.28 (ddt, *J* = 12.8, 9.2, 3.9 Hz, 1H), 1.03 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 131.6, 128.4, 128.4, 128.4, 122.7, 94.8, 83.5, 71.3, 54.2, 53.0, 41.8, 41.6, 34.9, 32.5, 30.3, 22.1, 17.8. i-**24** (diagnostic peaks only): ^1H NMR (400 MHz, $CDCl_3$) δ 5.38 – 5.11 (m, 2H), 4.05 – 3.93 (m, 1H), 3.91 – 3.76 (m, 1H).



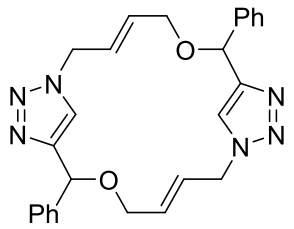
29a



29b

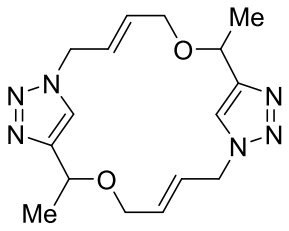
(5*R,6a*S**,10a*R**)-7,7-Dimethyl-1-phenyl-5-vinyl-6,6a,7,8,9,10-hexahydro-[1,2,3]triazolo[5,1-*a*]isoquinolin-10a(5*H*)-ol (29a), (5*S**,6a*S**,10a*R**)-7,7-dimethyl-1-phenyl-5-vinyl-6,6a,7,8,9,10-hexahydro-[1,2,3]triazolo[5,1-*a*]isoquinolin-10a(5*H*)-ol (29b).** Azides *trans*-**24** and i-**24** (1.12 g, 3.46 mmol) was dissolved in toluene (10 mL). The reaction mixture was heated at reflux for 24 h. The solvent was evaporated after cooling the reaction mixture to room temperature. The residue was purified by automated chromatography (silica, hexane:EtOAc/8:2) to give **29a** (0.63 g, 56%) and **29b** (0.19 g, 17%) (**29a**:**29b** 2.5:1). **29a**: Obtained as a colorless solid. R_f = 0.3 (50% EtOAc/hexanes); mp 162-164 °C; IR (neat) 3259 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{26}N_3O$ $[M + H]^+$ 324.2076, found 324.2039. ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.54 (m, 2H), 7.44 – 7.33 (m, 3H), 6.11 (ddd, *J* = 17.2, 10.2, 7.7 Hz, 1H), 5.50 (d, *J* = 17.2 Hz, 1H), 5.40 (d, *J* = 10.1 Hz, 1H), 4.84 (ddd, *J* = 11.7, 7.7, 5.5 Hz, 1H), 2.31 – 2.05 (m, 4H), 1.79 (qt, *J* = 14.0, 3.6 Hz, 1H), 1.55 – 1.46 (m, 1H), 1.44 – 1.34 (m, 1H), 1.31 – 1.15 (m, 3H), 1.06 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7, 136.6, 136.5, 132.6, 129.9, 128.3, 128.3, 118.7, 68.6, 62.7, 49.2, 40.9, 35.4, 33.2, 32.4, 26.5, 21.6, 17.7. **29b**: Obtained as a colorless oil. R_f = 0.25 (50% EtOAc/hexane); HRMS (ESI) *m/z* calcd for $C_{20}H_{26}N_3O$ $[M + H]^+$ 324.2076, found 324.2045; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.59 (m, 2H), 7.51 – 7.32 (m, 3H), 5.97 (ddd, *J* = 17.1, 10.5, 5.0 Hz, 1H), 5.29 (dd, *J* = 10.6, 1.6 Hz, 1H), 5.24 (ddt, *J* = 5.0, 3.3, 1.6 Hz, 1H), 4.93 (dd, *J* = 17.2, 1.7 Hz, 1H), 2.41 (ddd, *J* = 14.0, 12.8, 6.3 Hz, 1H), 2.37 – 2.28 (m, 1H), 1.93 (dt, *J* = 14.0, 1.6 Hz, 1H), 1.82 (qt, *J* = 13.8, 3.6 Hz, 2H), 1.59 (dd, *J* = 12.7, 1.7 Hz, 1H), 1.49 (dt, *J* = 13.5, 1.7 Hz,

1H), 1.39 (dt, *J* = 13.9, 3.5 Hz, 1H), 1.31 – 1.10 (m, 2H), 1.05 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.4, 136.5, 136.3, 132.4, 129.8, 128.3, 128.3, 117.7, 68.5, 58.8, 44.6, 40.9, 35.0, 32.9, 32.2, 23.8, 21.7, 17.7.



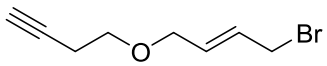
32

(1^4*Z*,8^4*Z*,5*E*,12*E*)-2,9-Diphenyl-1^1*H*,8^1*H*-3,10-dioxa-1(4,1),8(1,4)-ditriazolacyclotetradecaphane-5,12-diene (32). Azides *trans*-**3** and i-**3** (0.50 g, 2.20 mmol) were dissolved in a mixture of *tert*-BuOH/H_2O (1:1, 40 mL). $CuSO_4 \cdot 5H_2O$ (0.54 g, 2.20 mmol) and sodium L-ascorbate (0.87 g, 4.40 mmol) were added. The heterogenous mixture was stirred for 1 h. Then CH_2Cl_2 was added to dissolve the crude product and the aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL) and the combined organic layer was washed with aq NH_4OH (1 × 20 mL) and brine, and dried (Na_2SO_4). Filtration and concentration gave a residue, which was purified by automated chromatography (silica, CH_2Cl_2:MeOH 9:1) to give **32** (0.35 g, 70%) as a yellow oil. R_f = 0.5 (10% MeOH/CH_2Cl_2); IR (neat) 1453 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{27}N_6O_2$ [M + H]$^+$ 455.2195, found 455.2199. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.27 (m, 5H), 5.83 (tdd, *J* = 15.5, 12.9, 10.2, 7.2 Hz, 2H), 5.61 (s, 1H), 4.87 (d, *J* = 5.7 Hz, 2H), 4.04 (d, *J* = 4.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.8, 140.1, 132.5, 128.8, 128.3, 126.9, 125.4, 121.8, 76.4, 68.3, 51.9.



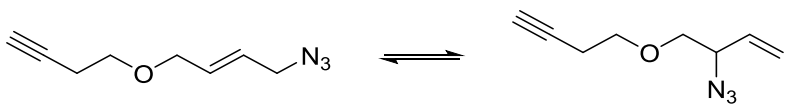
31

(1^4*Z*,8^4*Z*,5*E*,12*E*)-2,9-Dimethyl-1^1*H*,8^1*H*-3,10-dioxa-1(4,1),8(1,4)-ditriazolacyclotetradecaphane-5,12-diene (31). Following the general procedure for **32,** compound **31** (78%) was obtained as a yellow oil. R_f = 0.4 (10% MeOH/CH_2Cl_2); IR (neat) 1453 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{23}N_6O_2$ $[M + H]^+$ 331.1882, found 331.1898. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 5.92 (dt, *J* = 15.4, 6.2 Hz, 1H), 5.83 (dt, *J* = 15.5, 5.1 Hz, 1H), 5.04 – 4.88 (m, 2H), 4.73 (q, *J* = 6.6 Hz, 1H), 4.02 (dt, *J* = 4.9, 1.5 Hz, 2H), 1.53 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3, 132.9, 125.1, 120.8, 70.3, 68.0, 51.9, 21.5.



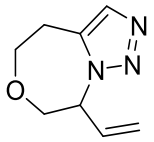
15aa

(*E*)-1-Bromo-4-(but-3-yn-1-yloxy)but-2-ene (15aa). Following the general procedure for **2a**, 3-butyn-1-ol (35, 2 g, 28.50 mmol), (*E*)-1,4-dibromobut-2-ene (12.19 g, 57 mmol), and NaH (1.14 g, 28.50 mmol) afforded **15aa** (1.42 g, 24%) as a colorless oil. R_f = 0.7 (10% EtOAc/hexanes); IR (neat) 2864 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 – 5.90 (m, 1H), 5.85 (dtt, *J* = 15.3, 5.5, 0.8 Hz, 1H), 4.08 – 4.00 (m, 2H), 4.00 – 3.91 (m, 2H), 3.57 (t, *J* = 6.9 Hz, 2H), 2.48 (td, *J* = 6.9, 2.7 Hz, 2H), 1.99 (t, *J* = 2.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.5, 128.9, 81.3, 70.4, 69.5, 68.5, 32.0, 20.0.



trans-**33** i-**33**

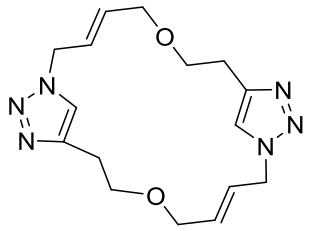
(*E*)-1-Azido-4-(but-3-yn-1-yloxy)but-2-ene (*trans*-33), 3-azido-4-(but-3-yn-1-yloxy)but-1-ene (i-**33).** Following the general procedure for **2**, (*E*)-1-bromo-4-(but-3-yn-1-yloxy)but-2-ene (**15aa**, 1.41 g, 6.90 mmol), and NaN_3 (1.35 g, 20 mmol) afforded a mixture of azides *trans*-**33** and i-**33** (0.87, 76%, 84:16) as a colorless oil. *trans*-**33** and i-**33** : R_f = 0.6 (10% EtOAc/hexanes); IR (neat) 2098 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_8H_{12}BrO$ $[M + H]^+$ 166.0980, found 166.1001. *trans*-**33**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 – 5.73 (m, 2H), 4.10 – 4.04 (m, 2H), 3.79 (d, *J* = 5.6 Hz, 2H), 3.58 (t, *J* = 6.9 Hz, 2H), 2.48 (td, *J* = 6.8, 2.7 Hz, 2H), 1.99 (t, *J* = 2.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.6, 126.0, 81.3, 70.5, 69.5, 68.5, 52.4, 20.0. i-**33** (diagnostic peaks only): ^1H NMR (400 MHz, $CDCl_3$) δ 5.52 – 5.22 (m, 2H), 3.63 (t, *J* = 7.0 Hz, 2H), 3.49 (dd, *J* = 10.1, 7.5 Hz, 1H).



34

8-Vinyl-4,5,7,8-tetrahydro-[1,2,3]triazolo[1,5-*d*][1,4]oxazepine (34). Following the general procedure of **12**, azides *trans*-**33** and i-**33** (0.13 g, 0.79 mmol) afforded **34** (0.11 g, 81%) as a colorless oil. R_f = 0.3 (50% EtOAc/hexanes); IR (neat) 2957 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_8H_{12}N_3O$ $[M + H]^+$ 166.0980, found 166.0977. ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, 1H), 6.13 (ddd, *J* = 17.2, 10.6, 4.6 Hz, 1H), 5.48 (dp, *J* = 4.9, 1.8 Hz, 1H), 5.35 (dd, *J* = 10.6, 2.0 Hz, 1H), 4.84 (ddd, *J* = 17.2, 2.0, 0.6 Hz, 1H), 4.31 (dd, *J* = 13.3, 3.4 Hz, 1H), 4.25 – 4.07 (m, 1H), 3.82

(dd, *J* = 13.4, 1.6 Hz, 1H), 3.53 (ddd, *J* = 12.5, 10.7, 1.9 Hz, 1H), 3.17 – 2.91 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6, 133.5, 132.8, 118.5, 72.8, 70.2, 65.3, 26.2.



35

(1^4*Z*,9^4*Z*,6*E*,14*E*)-1^1*H*,9^1*H*-4,12-Dioxa-1(4,1),9(1,4)-ditriazolacyclohexadecaphane-6,14-diene (35). Following the general procedure for compound **32,** compound **35** (78%) was obtained as a yellow oil. R_f = 0.4 (10% MeOH/CH_2Cl_2); IR (neat) 1552 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{23}N_6O_2$ $[M + H]^+$: 331.1882, found: 331.1884. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 5.92 – 5.74 (m, 2H), 4.94 (dq, *J* = 2.7, 1.3 Hz, 2H), 4.00 (dd, *J* = 2.0, 1.0 Hz, 2H), 3.78 – 3.63 (m, 2H), 3.01 (t, *J* = 5.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 132.6, 124.2, 121.5, 70.0, 69.6, 51.9, 26.8.

Chapter 2

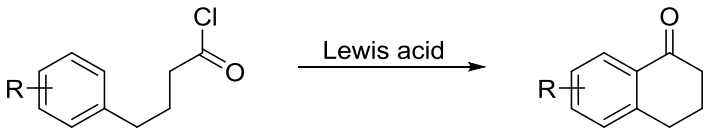
Intramolecular Friedel–Crafts acylation reaction promoted by hexafluoro-2-propanol

2.1 Introduction

Friedel–Crafts acylation

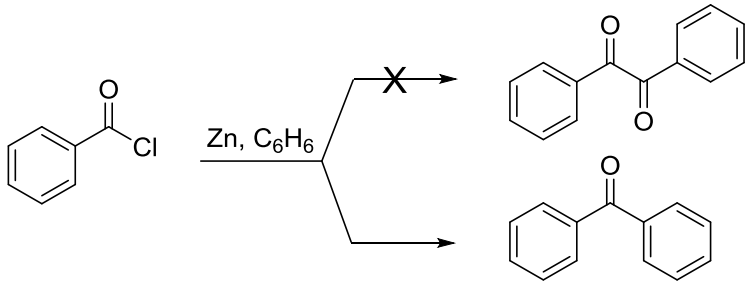
The Friedel–Crafts (FC) acylation is one of the most highly investigated reactions for carbon-carbon bond formation (Scheme 8).[52]

Scheme 8. FC acylation reaction



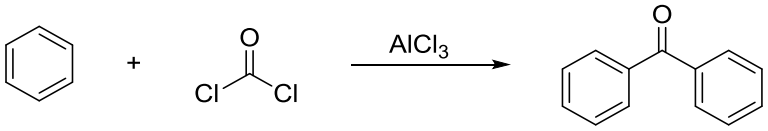
Grucarevic and Merz reported the first acylation reaction of aromatics with acid halides in 1873.[53] They used zinc dust to promote the reaction. Later, Zincke reported the treatment of benzene with benzoyl chloride using either copper, zinc, or silver in an attempt to prepare benzil, but instead obtained benzophenone (Scheme 9).[54] In 1876, Doebner and Stackman reported the formation of *o*-hydroxybenzophenone from phenol and (trichloromethyl)benzene using zinc oxide, and they observed zinc chloride at the end of reaction.[55] However, none of these researchers explained the importance of Lewis acids in acylation reaction until Charles Friedel and James Mason Crafts published their research in 1877.[52,56-58] Following this initial work, Friedel and Crafts showed that the reaction could be extended to various aromatic compounds, as well as alkyl and acyl chlorides or anhydrides in the presence of chlorides of metals like aluminum, zinc, and iron.[59]

Scheme 9. Zinc–catalyzed FC acylation[54]



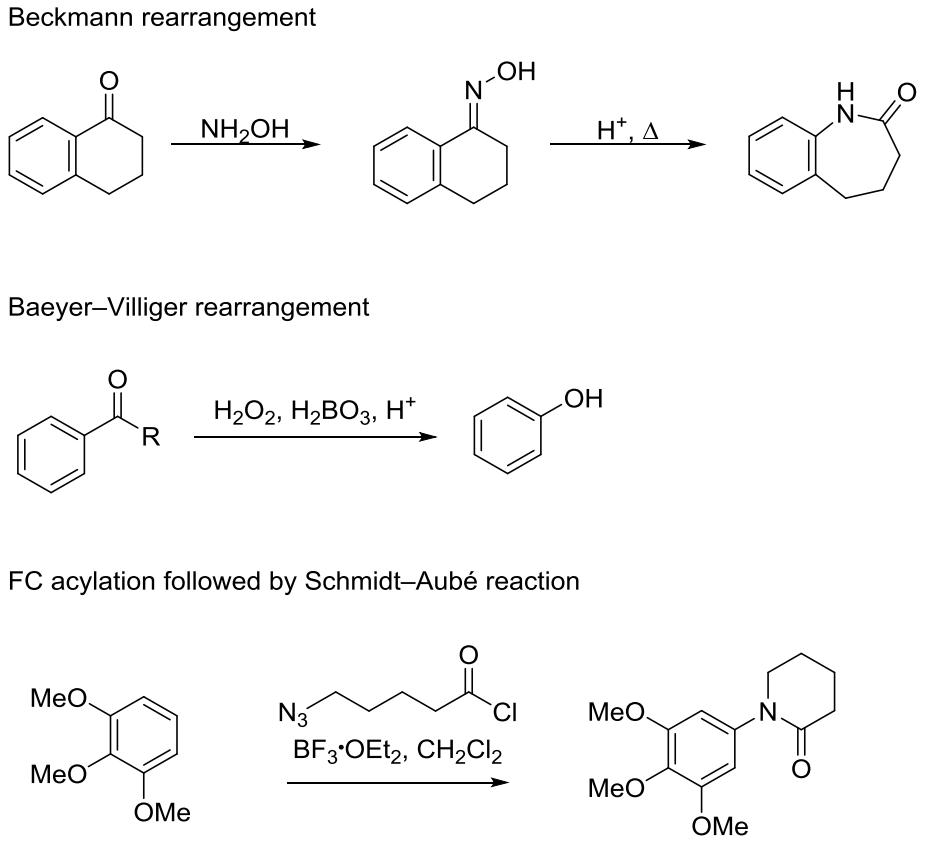
In an early paper by Friedel and Crafts, they reacted benzene and phosgene in presence of $AlCl_3$ which led to the formation of benzophenone and a small amount of benzoic acid (Scheme 10).[57] Further, Wilson and Fuller reacted benzene and higher equivalence of phosgene using $AlCl_3$ in hopes of obtaining anthraquinone, but rather they obtained benzoquinone.[60] Staudinger reported the reaction of anisole and oxalyl chloride using $AlCl_3$ led to the formation of corresponding benzyl derivative.[61] However, with polycyclic substrates, bridged ketones were obtained under Friedel–Crafts conditions with oxalyl chloride.[62]

Scheme 10. Early findings by Friedel and Crafts[57]



Introduction of acyl group into aromatic system connected with many useful transformation that can be performed easily. For example, tetralone derivatives can be easily converted to amines by Beckmann rearrangement; acetophenone into phenols using the Baeyer–Villiger rearrangement as well as FC acylation followed by Schmidt reaction to obtain lactams (Scheme 11).[63-65] The aromatic ketones are important by themselves as well.[63]

Scheme 11. Utilities of aromatic ketones in synthetic transformations



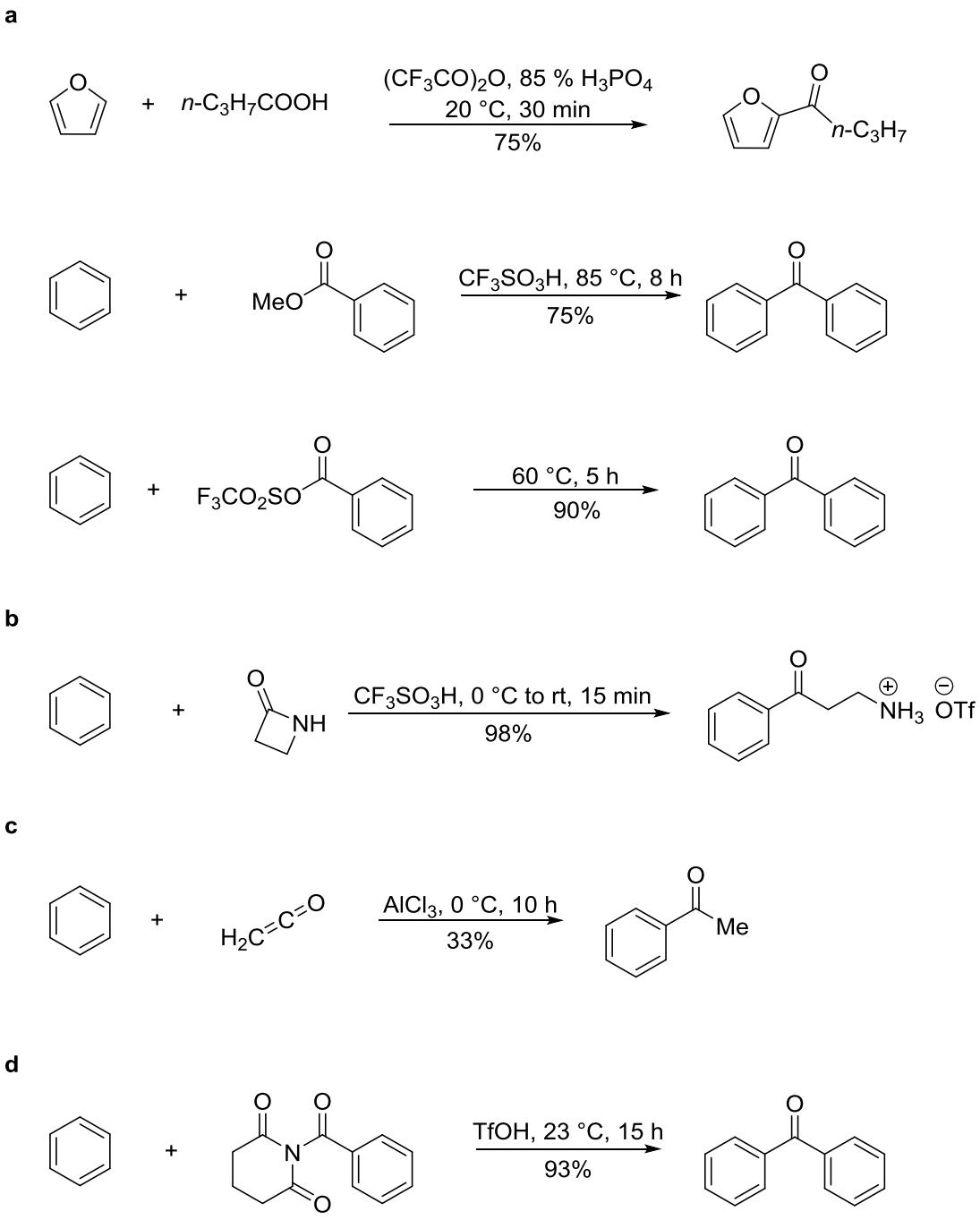
FC alkylation chemistry can also be used for carbon-carbon bond formation. However, the major limitation of Friedel–Crafts alkylation reaction is that the product after the first installation of alkyl group is more nucleophilic compared to the substrate, which lead to overalkylation.[66] This problem can be overcome by first performing a Friedel–Crafts acylation, followed by reduction of the keto group in product.[67,68]

Acylating agents in Friedel–Crafts reactions

The most commonly used acylating agents in FC acylation are acyl halides. The reactivity of acyl halides used with aluminum halides as catalysts was I > Br > Cl > F, however in case of boron halides as catalysts the order was acyl fluoride > acyl bromide > acyl chloride.[63] The other most

common acylating agents are anhydrides.[63] In FC acylation reaction, carboxylic acids, esters and mixed anhydrides were successfully used to give ketone products (Scheme 12a).[69-71] In addition, β-lactams were successfully used as acylating agents in the presence of triflic acid to give β-aminoaromatic ketone derivatives (Scheme 12b).[72] In the presence of $AlCl_3$, ketene has been used to acetylated benzene to give acetophenone (Scheme 12c).[73] Further, Szostak and coworkers reported FC acylation using twisted amides using triflic acid as catalyst (Scheme 12d).[74]

Scheme 12. Various acylating agents in Friedel–Crafts acylation[69-74]



Catalysts in Friedel–Crafts acylation

In addition to $AlCl_3$, other catalysts used in Friedel–Crafts acylation with acyl halides include $AlBr_3$, $TiCl_4$, $ZrCl_4$, $FeBr_3$, $SbBr_3$, P_2O_5, H_2SO_4, Zn, $ZnCl_2$, $CuCl_2$, $HgCl_2$.[75] The catalysts used

with anhydrides as acylating agents include BF_3, HF, $ZnCl_2$, H_3PO_4, $SnCl_4$, $SOCl_2$, $(CF_3CO)_2O$, CF_3COOH, $HClO_4$, $AgClO_4$.[75] Dermer and co-workers reported the relative efficiency of metal halides in catalyzing acylation of toluene by acetyl chloride as: $ZnCl_2 < BiCl_3 < TeCl_4 < TiCl_4 < SnCl_4 < TeCl_2 < FeCl_3 < SbCl_5 < AlCl_3$.[76]

Heterogeneous catalysts

Other catalysts like lanthanide trifluoromethanesulfonates alone[77] or microencapsulated on polyacrylonitrile[78] as reusable catalysts, and graphite as a solid catalyst[79] were used to promote FC acylation. Various classes of heterogeneous catalyst were used for FC acylation, including zeolites, metal oxides, clays, heteropoly acids and Nafion.[80] BEA zeolites are the most important zeolite catalyst for FC acylation both in academia and industries.[81] Many metal triflates like $La(OTf)_3$, $Ce(OTf)_4$, $Y(OTf)_3$ and $Zn(OTf)_2$ were used with SBA-15 by incorporation into mesoporous pores as catalyst.[82] Laszlo et al.[83-86] described the use of clays in FC acylation. As FC acylation catalyst iron(III) oxide, zinc oxide, tin(II) oxide, or molybdenum(VI) oxide with iron(III) oxide possessed the great activity.[87] Arata and co-workers shown that sulfated zirconia (SZ), prepared by treatment of zirconia with sulfuric acid or ammonium sulfate, exhibit good catalytic activity.[88] Heteropoly acids (HPAs), bronsted acids composed of heteropoly anions and protons as counterions, were successfully used as catalyst in FC acylation.[89] Nafion, a solid perfluorinated resinsulfonic acid, was also used as heterogeneous catalyst in FC acylation.[90-92]

Catalytic Friedel–Crafts acylation

The FC acylation could be described as a self-inhibitory reaction as the ketone product and catalyst can form a stable complex which requires the use of at least stoichiometric amount of catalyst for the reaction to go to completion.[93] In general, substoichiometric, catalytic reactions

need to be performed at high temperatures to promote the dissociation of the ketone-catalyst complex.[59,93]

Pivsa-Art et al. reported the acylation of 2-methoxynaphthalene by benzoyl chloride in the presence of 10 mol% of various Lewis acids (including $AlCl_3$, $FeCl_3$) at 160 °C and described the influence of Lewis acids on the regiochemical outcomes in product formation.[94] Le Roux and co-workers reported the acylation of toluene, xylene, mesitylene, naphthalene, anthracene, pyrene, and anisole using $BiCl_3$ (10 mol%) at 120 °C.[95] They recovered catalyst by converting it to a water-insensitive bismuth(III) oxychloride (BiOCl). The BiOCl can be used to carry out acylation reaction as procatalyst as it converts to active catalyst $BiCl_3$ upon reacting with acyl chloride in-situ.[95]

The antimony pentachloride-benzyltriethylammonium chloride complex ($SbCl_5$–TEBA) was reported to have catalytic activity in acylation of electron-rich arenes with acyl and sulfonyl chlorides.[96] The reactions were carried out using $SbCl_5$–TEBA (5 mol%) in boiling nitromethane to give ketone products in 37–96% yield. The advantages of this catalyst include ready access, minimal toxicity, reusability, insensitivity to atmosphere and moisture. Another antimony derivative, diphenylboryl hexachloroantimonate (Ph_2BSbCl_6) (25 mol%), was reported to catalyze FC acylation at room temperature.[97]

Harada et al. reported the acylation of activated substrates (aromatic ethers and alkyl arenes) catalyzed by a combination of Lewis acid and silver perchlorates.[98] In this reaction, acylation was carried out using gallium(III) trichloride (10 mol%) and silver perchlorate (10 mol%) to afford ketones in 80-100% yield at room temperature. In addition, good results were achieved in FC acylation by a combination of antimony pentachloride (4 mol%) and lithium perchlorate (100

mol%) in refluxing methylene chloride.[99] Arai et al. reported the catalytic efficiency of combination of niobium pentachloride (1 mol%) and silver perchlorate (3 mol%) at 80 °C in FC acylation reactions.[100]

Furstner et al. reported the late-transition metal salts as catalysts in acylation of arenes and heteroarenes using anhydrides.[101] Their rationale of using a late transition metal was that the mismatch between soft metal center and the hard ketone oxygen of products prevents the kinetically inert complex formation and results in catalytic turnover. Thus, acylation of various aromatic substrates were performed in refluxing DCM in presence of $(PhCN)_2PtCl_2$ (2.5 mol%) and $AgSbF_6$ (5 mol%). However, *N*,*N*-dimethylaniline and indole were inert under this condition, probably due to inhibition of cationic platinum(II) species by coordination with the nitrogen atom in these substrates.

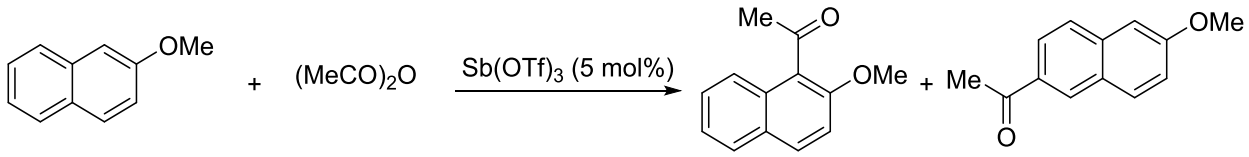
The use of catalytic bismuth(III) triflate in FC acylation was reported by Desmurs.[102] Bismuth(III) triflates (10 mol%) was used to acylate both activated (electron-rich) and deactivated (electron-poor) aromatic compounds under heating condition to give product ketones in high yield (78%−95%) using acyl chlorides or anhydrides as acylating agents. The combination of titanium(IV) monochlorotriflate ($TiCl(OTf)_3$) (1 mol%) with triflic acid (10 mol%) was reported to be an efficient catalyst in FC acylation at room temperature.[103]

Similarly, the combination of hafnium triflate (10 mol%) and triflic acid (10 mol%) was used efficiently in acylation of benzene and unactivated benzenes such as chlorobenzene and fluorobenzene at 80−120 °C.[104] The FC acylation of aromatics with acids have been reported to be catalyzed by bismuth triflate (10 mol%) in the presence of trifluoroacetic anhydride or heptafluorobutyric anhydride.[105]

Kawada et al. reported FC acylations promoted by 20 mol% of lanthanide trifluoromethane sulfonate ($Ln(OTf)_3$) at 50 °C.[77] Specifically, ytterbium triflate (20 mol%) catalyzed acetylation reactions of various aromatic systems using acetic anhydride as acylating agent. It has been shown that catalyst could be recovered and reused in further reaction without loss of efficiency. Scandium triflate (20 mol%) was also reported as catalyst in FC acylation of arenes using acyl chloride or anhydrides as acylating agents.[106] The catalyst could be recovered and reused. In addition, combination of lanthanide triflates (20 mol%) with lithium perchlorates was reported to have greater catalytic activity than lanthanide triflate alone.

An interesting result was obtained when lithium perchlorate was used as an additive while acetylating 2-methoxynaphthalein with acetic anhydride using antimony(III) triflate (Table 3). When the reaction was performed in nitromethane without an additive, product **a** was obtained preferentially. However, the regioselectivity changed when the same reaction was carried out in the presence of lithium perchlorate (600 mol%), and product **b** was obtained in 93% yield. The rationale given for this result was that the acetyl group migrates from kinetic product **a** to give thermodynamic product **b** during the reaction. It was reported that indium(III) triflate (1 mol%) in combination with lithium perchlorate could be efficiently used in FC acylation reactions.[107]

Table 3. Effect of additive on regiochemical outcome of products[108]



a **b**

Additive	Solvent	T (°C)	Yield (%)	Product distribution (%)	
				a	**b**
–	$MeNO_2$	rt	81	95	5
$LiClO_4$	$MeNO_2$	50	93	0	100

Fillion and co-workers reported the intramolecular FC acylation of benzyl Meldrum's acids catalyzed by $Sc(OTf)_3$ (12 mol%) under reflux condition in nitromethane to give 1-indanones.[109] In addition, the method was extended to the synthesis of 1-tetralone and 1-benzosuberones.[110] Xiao et al. reported the FC acylation catalyzed by $Cu(OTf)_3$ (10 mol%) in an ionic liquid, [bmim][BF_4] (bmim = 1-butyl-3-methylimidazolium) at 80 °C.[111]

Cui et al. showned that $Bi(NTf_2)_3$ (1 mol%) catalyzed intramolecular FC acylation reactions of aryl butyric acids to give 1-tetralones at 180 °C.[112] In addition, chroman-4-ones and thiochroman-4-ones were obtained under similar conditions. Ytterbium tris(perfluoroalkanesulfonyl)methide (10 mol%) was reported as effective catalyst in FC acylation of arenes with anhydrides.[113] Kobayashi and coworkers reported that gallium nonafluorobutanesulfonate [$Ga(OTf)_3$] (5 mol%) was efficient catalyst in the acylation of activated and deactivated aromatic compounds under reflux condition with acyl chlorides.[114]

Earle and co-workers reported various metal bis[(trifluoromethyl)sulfonyl]amide complexes (5−15 mol%) as efficient catalyst in FC acylation reaction.[115] Hafniumtetra[bis(perfluorooctanesulfonyl)amide] (1 mol%) in fluorous solvent was reported to catalyze FC acylation at 70−120 °C.[116] It was reported that indium (20 mol%) catalyzed benzoylation of various aromatic systems at 100 °C in dioxane.[117] Deactivated aromatic systems like chlorobenzene and bromobenzene were inactive under these conditions. Dominguez et al. reported the FC acylation of electron-rich aromatic systems catalyzed by iodine (2 mol%) under

reflux condition.[118] Halobenzenes were benzoylated selectively at para-position catalyzed by iron(III) sulfate (1 mol%) by different benzoyl chlorides under high temperature (135–150 °C).[119]

Intramolecular FC acylation

Intramolecular FC acylation leads to the formation of benzocyclic ketones such as 1-indanones, 1-tetralones, 1-benzosuberones, and related compounds (Figure 9).[75,120,121]

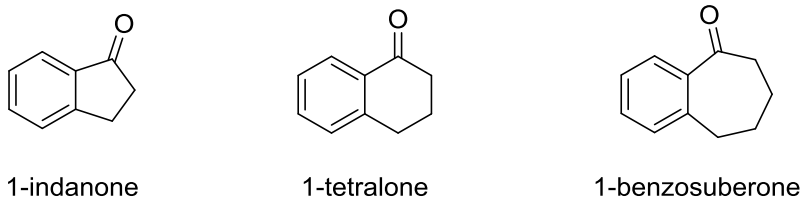


Figure 9. General products of intramolecular FC acylation reaction

The products of intramolecular FC acylation reactions have been utilized for the synthesis of biologically active natural products and therapeutically useful compounds (Figure 10). Substituted 1-tetralones have been used for the synthesis of natural product palmarumycin CP_1 and series of antiapoptotic Bcl-2 family proteins inhibitors for their activity as anticancer agents.[122,123] Similarly, substituted 1-indanones have been used for the synthesis of ribasine and the angiogenesis inhibitor NM-3.[124,125]

General aspects of the intermolecular FC acylation reaction applies to the intramolecular reaction as well.[121] In general, 1-tetralones are easier to form than to 1-indanones and 1-benzosuberones by FC acylation reactions.[110] In case of intramolecular FC acylation, carboxylic acids,[126-128] acid chlorides,[129,130] ketenes,[131,132] isocyanates,[133-135] isothiocyanates,[136,137] β-lactams,[72] and cyclic anhydrides[138-141] have been used as acylating agents. Most frequently used

catalyst in intramolecular FC acylation reactions include pyrophosphoric acid, Lewis acids, protic acids and heterogenous catalysts.[91,92,120]

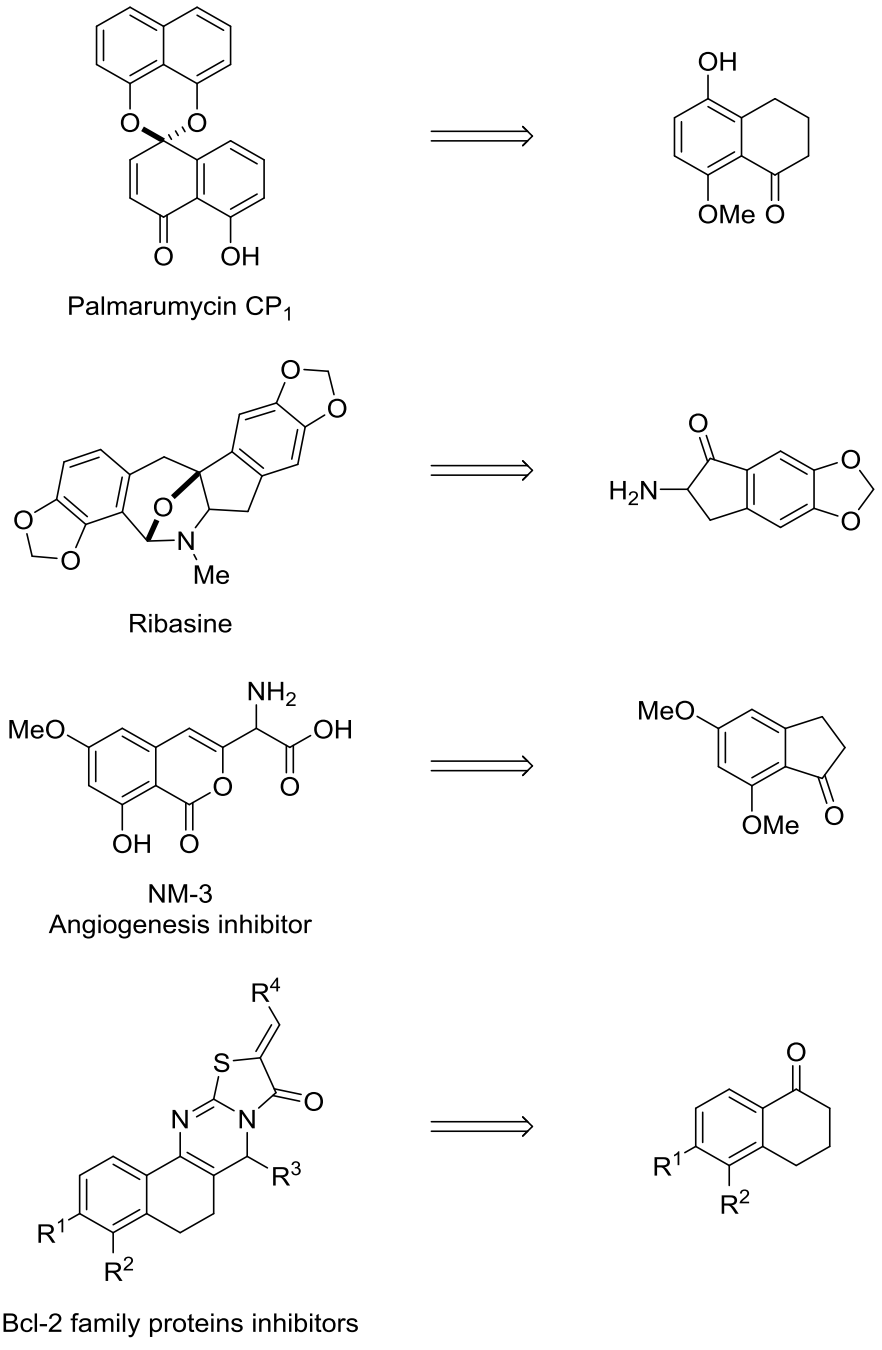


Figure 10. Aryl ketones as synthetic precursors to natural product synthesis and therapeutic agent synthesis.

Commonly used solvents in FC acylation reactions include carbon disulfide, carbon tetrachloride, dichloromethane, 1,2-dichloroethane, nitrobenzene and nitroalkanes.[63,75] In addition, researchers have used ionic liquids as reaction media.[111,142] In general, protic solvents are not compatible with FC acylation due to its nucleophilic nature that could compete with arenes to react with acylating agents. However, hexafluoro-2-propanol has been used in FC reactions due to its low nucleophilicity.[143]

Hexafluoro-2-propanol (HFIP)

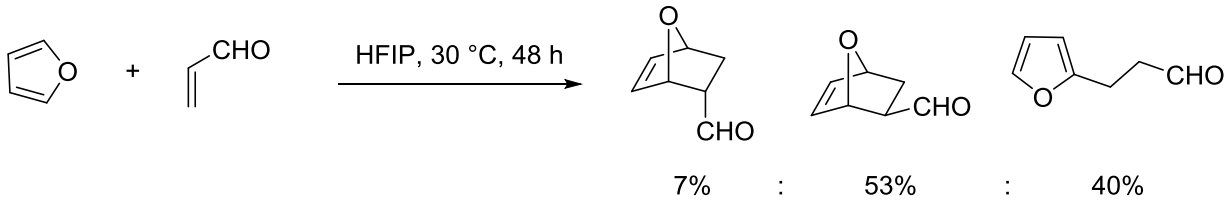
HFIP is one of the most commonly used fluorinated alcohols due to its low cost and commercial availability.[143,144] HFIP is a polar solvent with high ionizing power and low nucleophilicity.[143] In addition, it is a poor hydrogen bond acceptor while a very strong hydrogen bond donor (Table 4).[143]

Table 4. Properties of HFIP and isopropanol[143,145-150]

Property	HFIP	isopropanol
Melting point (°C)	-4	-89.5
Boiling point (°C)	58.6	82.5
Density (g/mL)	1.61	0.781
pKa	9.3	17
Polarity, P_s	11.08	7.85
Ionizing power (Y_{OTs})	3.79	-2.83
Nucleophilicity (N_{OTs})	-4.23	0.2
Dielectric constant (ε)	16.7	19.4
Polarizability	0.65	0.48
Dipole moment (μ)	2.03	1.68
Hydrogen-bond donor (α)	1.96	0.76
Hydrogen-bond acceptor (β)	0.03	0.84

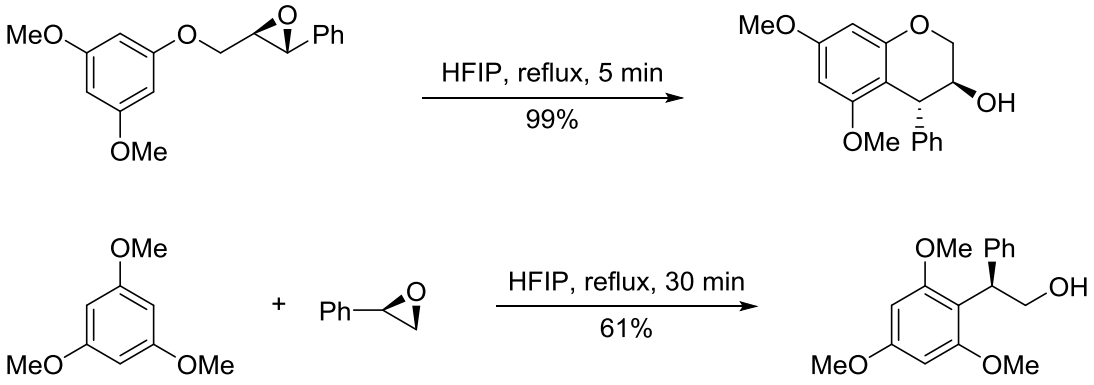
In 1993, Cativiela et al. studied the advantage of the HFIP solvent in Diels–Alder reactions to obtain good regio- and endo/exo selectivities.[151] Interestingly, when they reacted furan and acrolein in HFIP, in addition to Diels–Alder products oxanorbornene derivatives, they also observed 3-(2-furyl)propanol, as Friedel–Crafts-type alkylation product (Scheme 13).

Scheme 13. Diels-Alder and Friedel–Crafts alkylation in HFIP



Li and Qu reported the regio- and stereoselective intra- and intermolecular Friedel–Crafts alkylation between electron-rich arenes and epoxides in HFIP at reflux condition (Scheme 14).[152] They attributed the weak acidity and high ionizing power of HFIP as being responsible for its catalytic activity in this reaction.

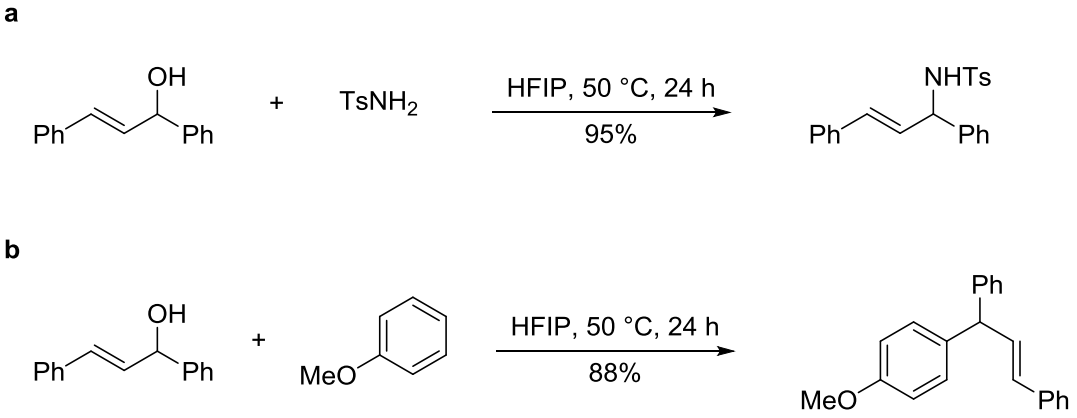
Scheme 14. Intra- and intermolecular Friedel–Crafts alkylation between arenes and epoxides



Trillo et al. reported the direct allylic substitution of allylic alcohol in HFIP as reaction media (Scheme 15a).[153] In their studies, when they reacted (*E*)-1,3-diphenylprop-2-en-1-ol with anisole

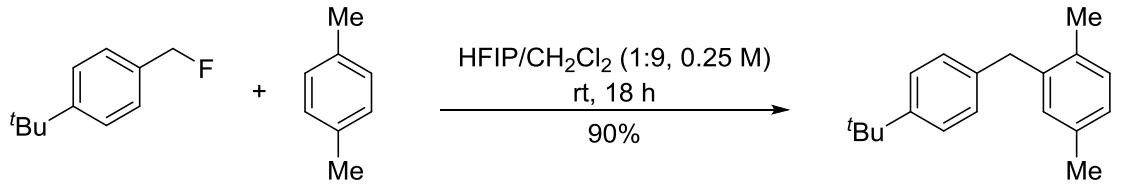
in HFIP at 50 °C, the *para*-substituted Friedel–Crafts alkylation product was obtained in 88% yield (Scheme 15b).

Scheme 15. Friedel–Crafts-type alkylation in HFIP

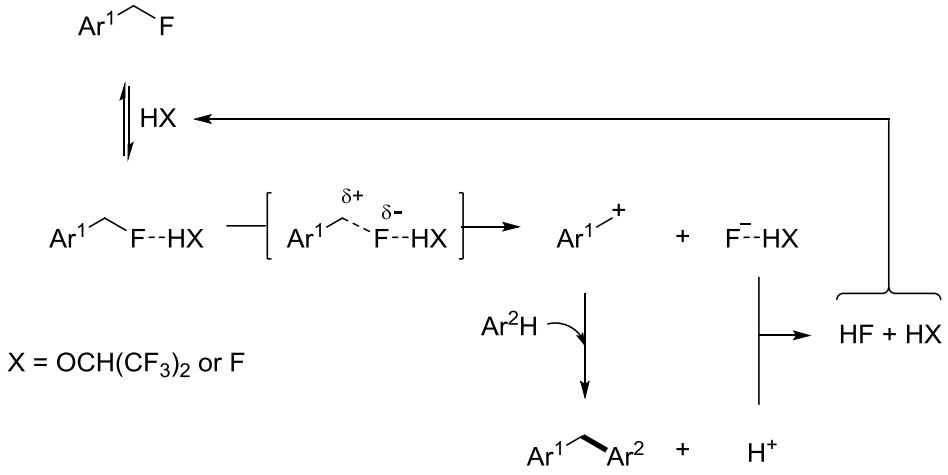


In 2014, Paquin and co-workers reported the Friedel–Crafts benzylation reaction between benzyl fluoride and arenes catalyzed by HFIP (Scheme 16).[154] They proposed a mechanism where by HFIP activates the C–F bond through hydrogen bonding. HFIP was also used as a medium to promote an FC reaction catalyzed by Cu[155,156] and Li[157] Lewis acids. Recently, Khaledi reported Friedel–Crafts reaction between arenes and heteroarenes with a benzyl chloride in an HFIP–water two-phase system.[158]

Scheme 16. Friedel–Crafts benzylation catalyzed by HFIP[154]



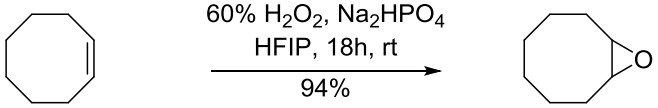
Mechanistic hypothesis



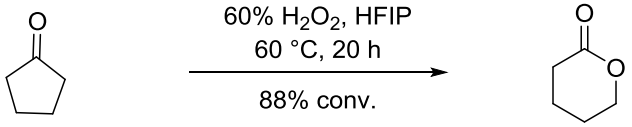
In addition, HFIP has been efficiently used for oxidation reaction with H_2O_2 (epoxidation of olefins, transformation of sulfides into sulfoxides, and Baeyer-Villiger oxidation) or sodium hypochlorite,[159-162] aza-Michael reaction,[163] protection[164] and deprotection[165] (Scheme 17).

Scheme 17. Oxidation, aza-Michael, protection and deprotection reactions promoted by HFIP[159-165]

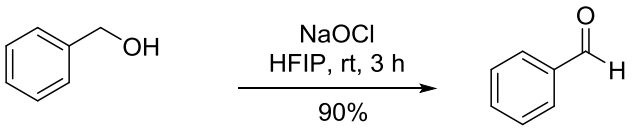
a



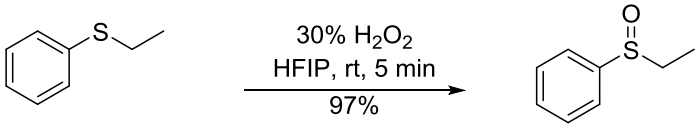
b



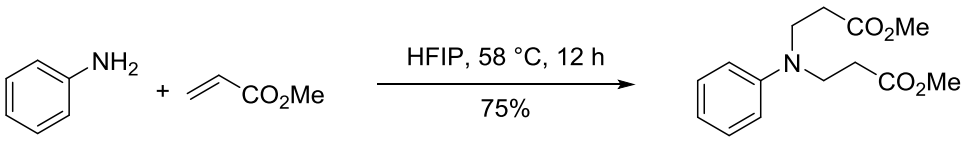
c



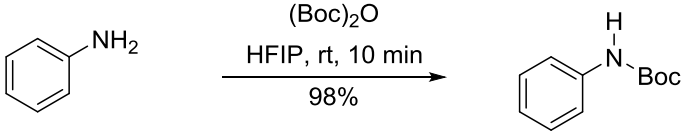
d



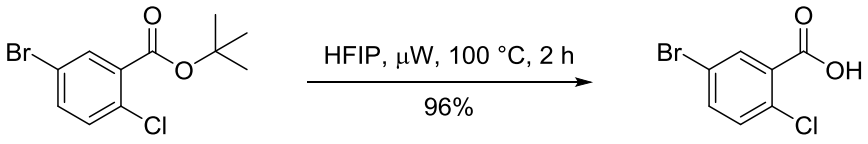
e



f



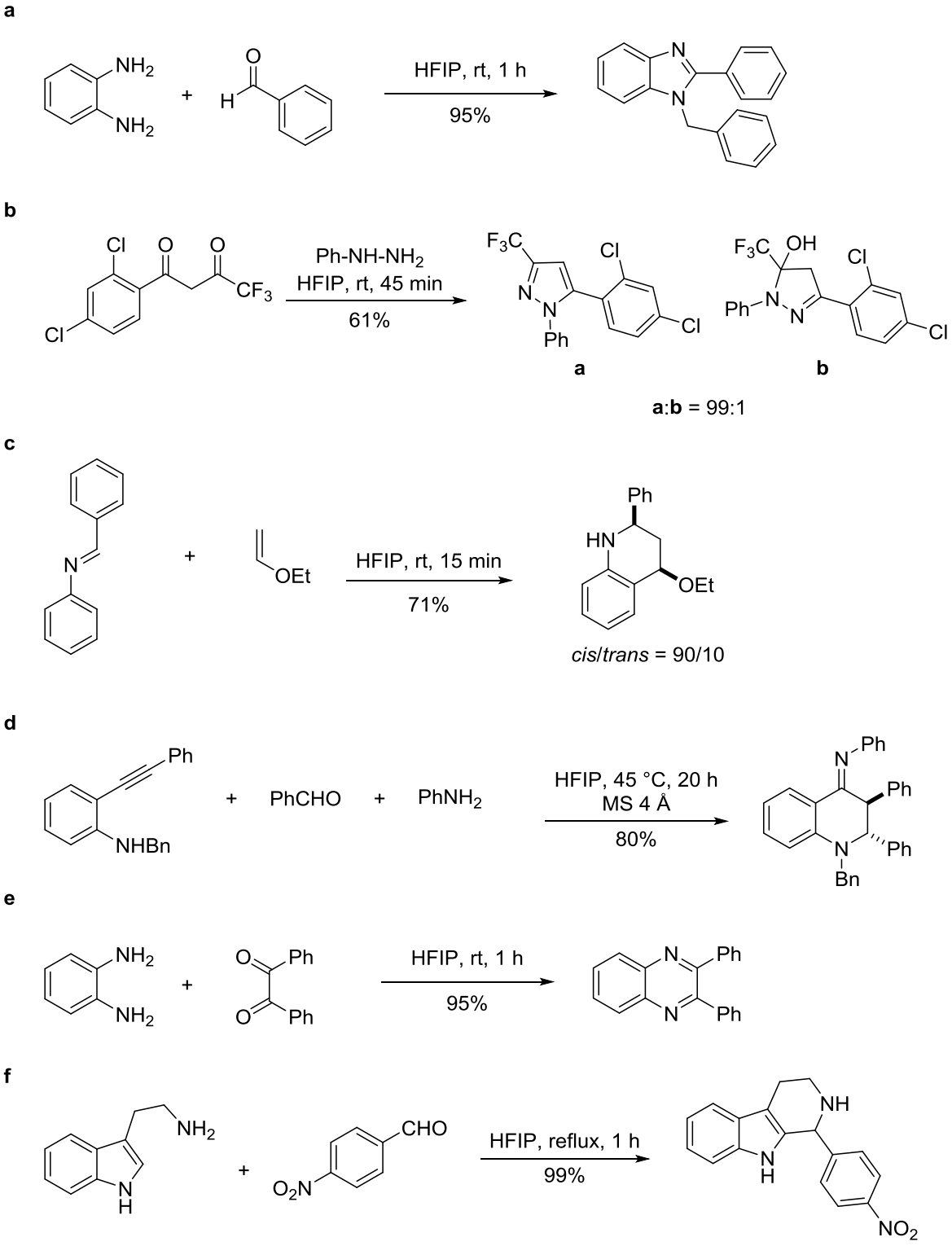
g



Chakraborti and co-workers reported the cyclocondensation of *o*-phenylenediamine with aldehyde to give 1,2-disubstituted benzimidazoles promoted by HFIP at room temperature (Scheme 18a).[166] Fustero et al. reported HFIP promoted regioselective pyrazoles formation from reaction of 1,3-diketones with hydrazines (Scheme 18b).[167] HFIP has been utilized to promote imino-Diels-Alder reactions to synthesize tetrahydroquinolines from the reaction between *N*-arylaldimine and alkyl vinyl ethers without Lewis acid under mild and neutral conditions (Scheme 18c).[168]

Saito and co-workers reported the synthesis of trans-2,3-disubstituted 2,3-dihydro-4-imino-quinolines from ortho-alkynylanilines, aldehydes and amines via the three-component alkyne-imine metathesis in HFIP without any additional catalysts (Scheme 18d).[169] Khaksar and Rostamnezhad reported the synthesis of quinoxaline derivatives from 1,2-diamines and 1,2-dicarbonyl compounds using HFIP at room temperature (Scheme 18e).[170] Wang et al. reported the Pictet-Spengler reaction between tryptamine derivatives and aldehydes or activated ketones to give tetrahydro-β-carbolines promoted by HFIP (Scheme 18f).[171]

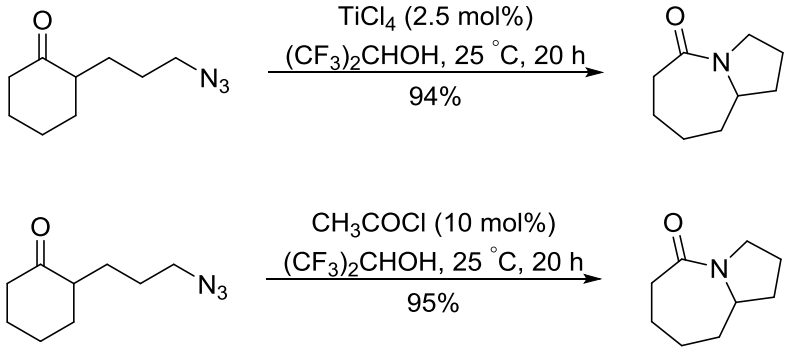
Scheme 18. HFIP-promoted heterocycles synthesis[166-171]



2.2 Results and discussion

As discussed earlier, an FC acylation reaction generally requires at least a stoichiometric amount of catalyst due to complex formation between product and catalyst, which leads to product inhibition. Most existing methods suffer from use of high temperature and requires water workup, which generates acidic waste. Similarly, the intramolecular Schmidt reaction suffered from the use of superstoichiometric amounts of catalyst due to product inhibition. Recently, Aubé and co-workers utilized the strong hydrogen-bond donating solvent, HFIP, to overcome the product inhibition in these reactions and showed that high yields were achieved with the use of substoichiometric catalysts (Scheme 19).[172] Based on this work, we thought to explore the utility of HFIP in promoting FC acylation reaction.[173] This project was done in collaboration with Dr. Hashim Motiwala.

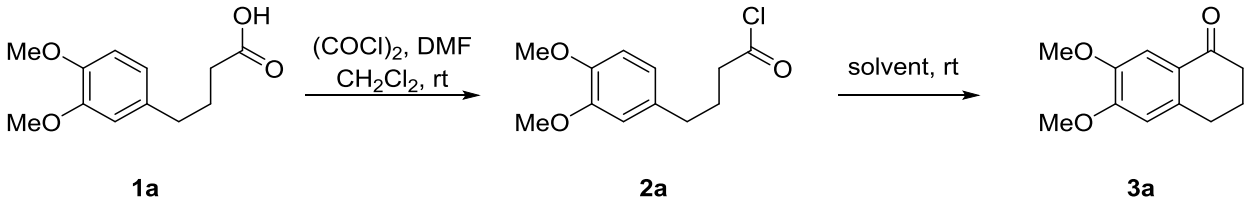
Scheme 19. HFIP in an intramolecular Schmidt reaction



We began by studying commercially available electron-rich 4-(3,4-dimethoxyphenyl)butanoic acid **1a** as a typical substrate for the intramolecular FC acylation. The corresponding acid chloride was obtained by oxalyl chloride treatment of **1a** in DCM. The crude acid chloride **2a** was dissolved in HFIP and the reaction allowed to stir for 2 h at room temperature. Evaporation of solvent followed by chromatographic purification led to product 6,7-dimethoxy-1-

tetralone **3a** in 95% yield (Table 5, entry 1). Different molar concentration of substrate had little effect on the product yield (Table 5, entries 1−3). Using DCM as solvent, different stoichiometries of HFIP was examined (Table 5, entries 3−6). In each case, comparable product yields were obtained in similar reaction time. Other representative solvents were screened in a 4:1 ratio of solvent: HFIP (Table 5, entries 7−10). The results reflected a qualitative decrease in reaction rate. Especially, THF had a deleterious effect on product yield. This is likely due to strong hydrogen bond acceptor effect of THF, which could form hydrogen bond with HFIP.[174,175]

Table 5. Exploration of reaction conditions[a]



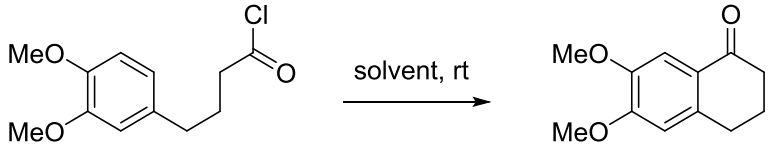
1a **2a** **3a**

entry	solvent	HFIP (equiv)	time (h)	yield of **3a**[b]
1	HFIP (0.20 M)		2	95
2	HFIP (0.40 M)		2	97
3	HFIP (1.2 M)		2	95
4	DCM/HFIP (4:1)	9.5	2	96
5	DCM/HFIP (8.4:1)	5.0	2	95
6	DCM/HFIP (22.8:1)	2.0	3	93
7	CH_3CN/HFIP (4:1)	9.5	6	93
8	CH_3NO_2/HFIP (4:1)	9.5	6	91
9	$C_6H_5CF_3$/HFIP (4:1)	9.5	4	94
10	THF/HFIP (4:1)	9.5	6	34

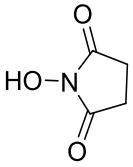
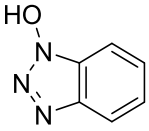
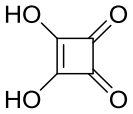
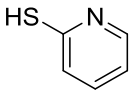
[a]The acid **1a** (1.0 equiv) was converted to **2a** using oxalyl chloride (2.0 equiv) and catalytic DMF in DCM under N_2 atmosphere for 30 min. The reaction mixture was concentrated under N_2 and vacuum; crude **2a** was dissolved in the solvent(s) noted and stirred at rt for a specified period. [b]Isolated yield of purified **3a** based on starting acid. Product were ≥96% pure by NMR except for entry 10, which was ca. 85% pure.

Screening of alternative reagents, other alcohols and related agents that might, in principle, be expected to similarly promote FC acylation reactions of **1a**, were performed. *N*-Hydroxysuccinimide (NHS) and 1-hydroxybenzotriazole (HOBt), commonly used in peptide chemistry, gave low yield while perfluorophenol (PFP) gave moderate yield (Table 6, entries 1–3).[176] Squaric acid failed to give appreciable product yield (Table 6, entry 4). Aryl thiols, utilized in native chemical ligation,[177] did not give any product (Table 6, entries 5–6). Of the various fluorinated alcohols investigated, only HFIP (Table 6, entry 8) and perfluoro-*tert*-butanol (PFTB, Table 6, entry 9) gave good yields. No product was obtained from the treatment of *i*-PrOH (Table 6, entry 12). From these results, it is clear that the ability to promote the FC acylation is not depend on p*K*a rather it is depend on hydrogen bond donating ability of electron-poor alcohols (i.e., *i*-PrOH gave no product vs. HFIP and PFTB gave excellent yields).

Table 6. Comparison with alternative reagents[a]



2a **3a**

entry	reagent	amount of reagent	solvent	p*K*a	time	NMR yield of **3a** (%)[b]
1	 NHS	5.0 equiv[c]	DCM	6.1	4 h	21
2	 HOBt	5.0 equiv[c]	DCM	4.6	4 h	0
3	C_6H_5OH (PFP)	5.0 equiv[c]	DCM	5.5	4 h	69
4	 Squaric acid	5.0 equiv[c]	DCM	0.55	6 h	5
5	 2-Mercaptopyridine	5.0 equiv[c]	DCM	-1.0	4 h	0
6	$HSC_6H_4CH_2CO_2H$ (MPAA)	5.0 equiv[c]	DCM	6.6	4 h	0
7	CF_3CH_2OH (TFE)	0.50 mL	–[d]	12.4	4 h	31
8	$(CF_3)_2CHOH$ (HFIP)	0.50 mL	–[d]	9.3	45 min	95
9	$(CF_3)_3COH$ (PFTB)	0.50 mL	–[d]	5.4	45 min	>98[e]
10	$C_6H_5C(CF_3)_2OH$	0.50 mL	–[d]	–	4 h	60
11	CF_3CH_2SH (TFET)	0.50 mL	–[d]	7.3	4 h	7[f]
12	$(CH_3)_2CHOH$ (*i*-PrOH)	0.50 mL	–[d]	16.5	4 h	0[g]

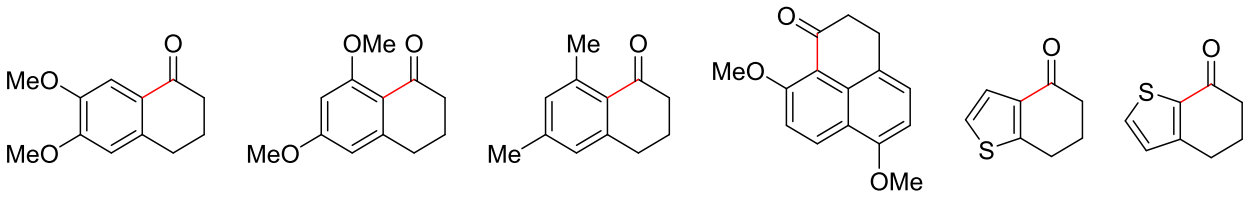
[a]Reaction was run on 0.100 mmol scale of **1a**. Concentration of **2a** was ca. 0.20 M. [b]Nitromethane was used as an internal standard. [c]Reagent (5.0 equiv) was used with DCM (0.50 mL) as solvent. [d]Reagent (0.50 mL) was used as a solvent. [e]Only product peaks were observed in a crude ^{1}H NMR. [f]A complex mixture was observed in a crude ^{1}H NMR. [g]Instead of product **3a**, *iso*-propyl ester was obtained in 92% yield.

After screening various reagents, it was found that only perfluoro-*tert*-butanol gave results comparable to HFIP. However, due to the high cost of perfluoro-*tert*-butanol (ca. 36× the cost of HFIP; Oakwood Products), we chose to use neat HFIP for our standard condition ([substrate] = 0.40 M).

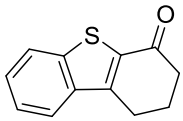
The scope of this methodology was explored utilizing variety of different carboxylic acids (Figure 11). Both arenes and heteroarenes gave six-membered ketones in good yields (**3a**–**3u**). Thus, various tetralones (**3a**–**3h**), chromanone (**3i**), thiochromanones (**3j**–**3m**), thioxanthenone (**3n**), and anthracenone (**3o**) were obtained from their corresponding acids in good to excellent yields. In general, six-membered rings in an intramolecular FC acylation are easier to form than over five- and seven-membered rings.[110]

In our conditions, seven-membered ketone products were obtained in good yields (**3v**–**3ab**). However, five-membered ketone product, thiophene fused cyclopentanone (**3ac**), obtained in poor yield. Fluorenones and related ketones (**3af**–**3am**) were obtained in good yields from their corresponding acids.

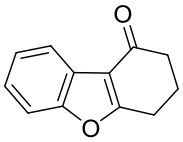
The reaction was also scaled up to gram scale. Thus, **3a** was obtained in 83% yield from 1.14 g (5.0 mmol) of **1a** in 1.6 mL of HFIP (which corresponds to 3 equiv) in 3 h.



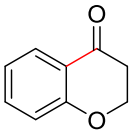
3a (97%) **3b** (86%) **3c** (73%) **3d** (51%) **3e** (81%) **3f** (72%)



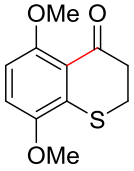
3g (99%)



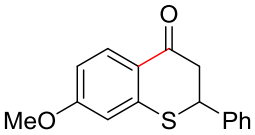
3h (90%)



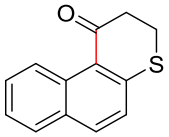
3i (70%)



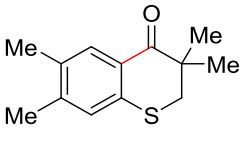
3j (53%)



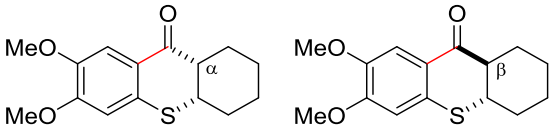
3k$_p$ + 3k$_o$
(75%; 82:18)



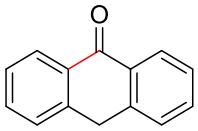
3l (92%)



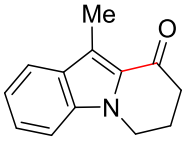
3m$_p$ + 3m$_o$
(96%; 64:36)



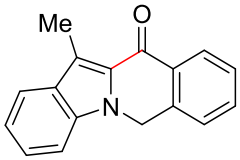
3n$_\alpha$ + 3n$_\beta$
(99%; 93:7)



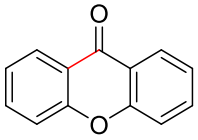
3o (77%)



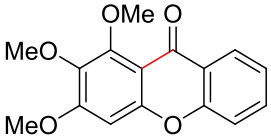
3p (72%)



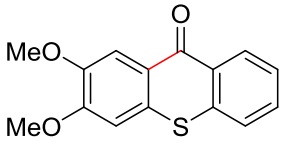
3q (73%)



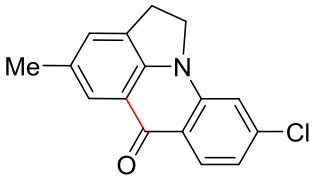
3r (77%)



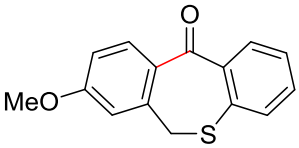
3s (93%)



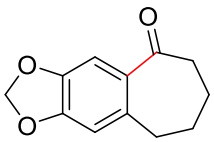
3t (93%)



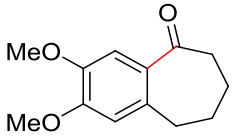
3u (82%)



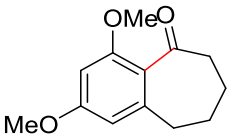
3v (81%)



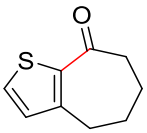
3w (59%)



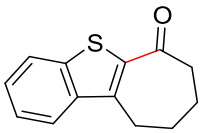
3x (56%)



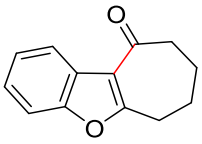
3y (61%)



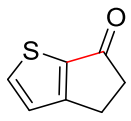
3z (72%)



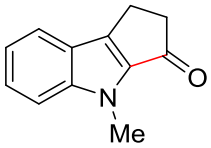
3aa (68%)



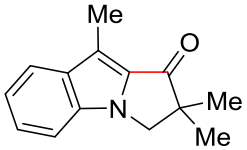
3ab (72%)



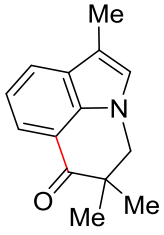
3ac (14%)

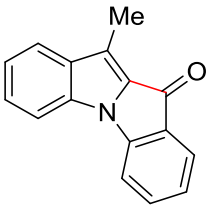


3ad (71%)



3ae$_2$ + 3ae$_7$
(78%; 85:15)





3af (87%)

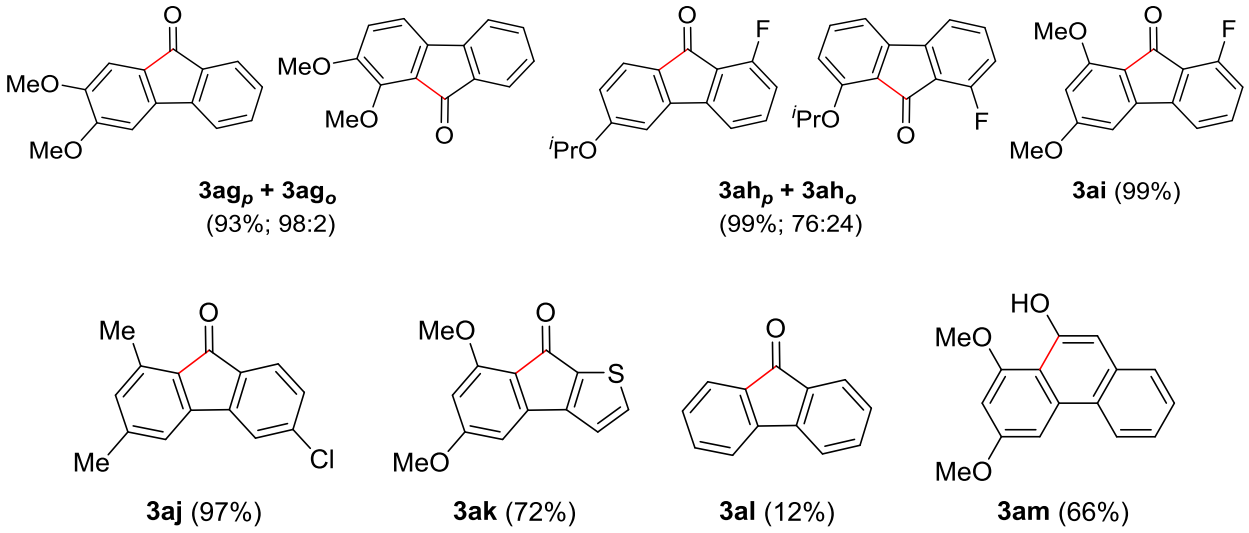
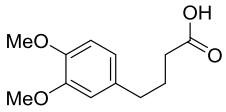
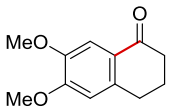
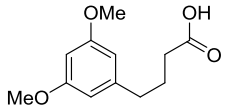
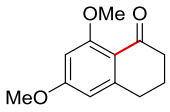
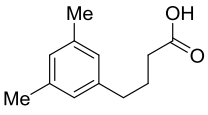
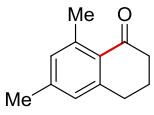
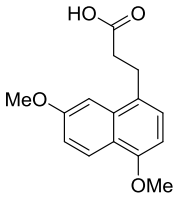
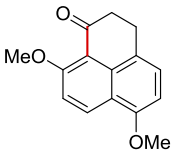
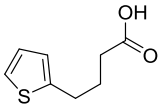
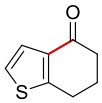
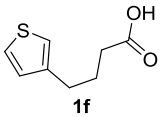
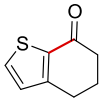
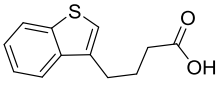
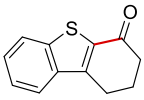
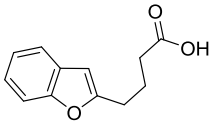
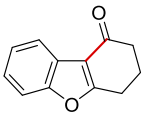
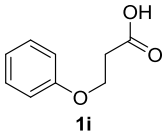
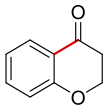
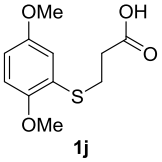
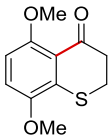


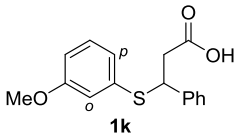
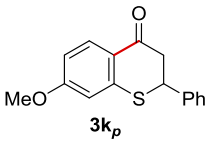
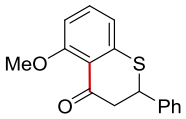
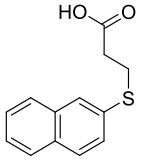
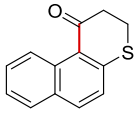
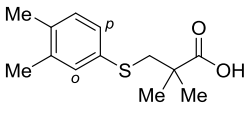
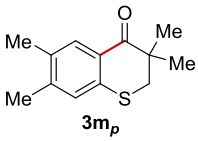
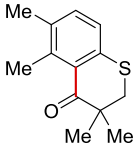
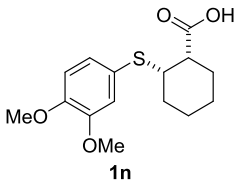
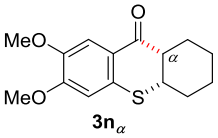
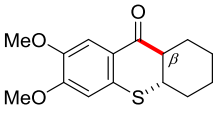
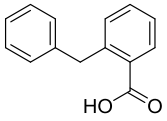
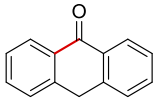
Figure 11. Yields and ratios of ketone products synthesized using standard conditions (Table 5, entry 2)

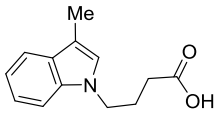
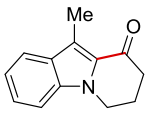
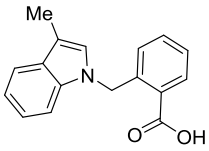
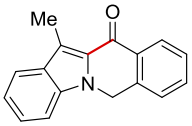
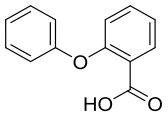
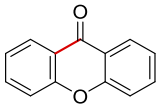
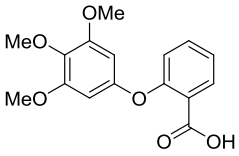
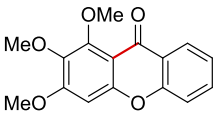
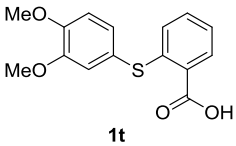
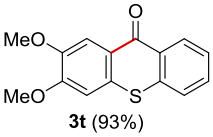
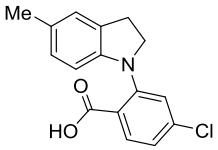
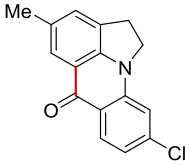
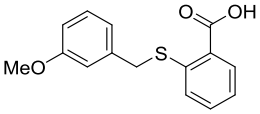
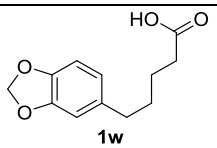
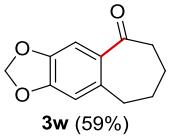
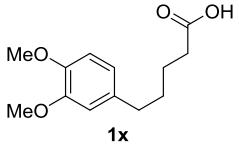
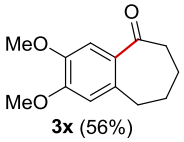
The results in Figure 11, obtained from current methods are compared with those obtained from traditional Friedel–Crafts acylation reactions (Table 7). This exercise suggests that the current methodology seems to have a similar scope with that of traditional methods.

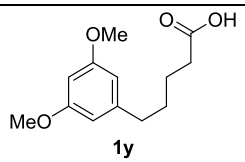
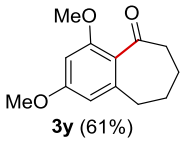
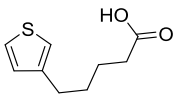
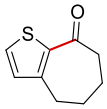
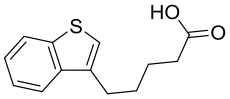
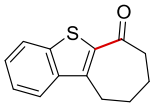
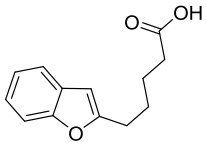
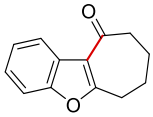
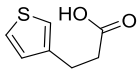
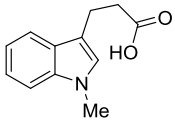
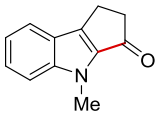
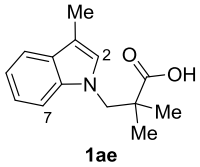
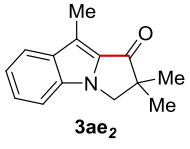
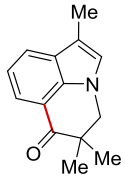
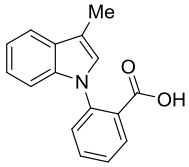
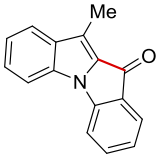
Table 7. Comparison of product yields obtained from this work (Figure 11) compared to that reported in the literature, along with their corresponding reaction conditions.

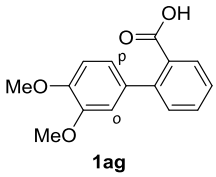
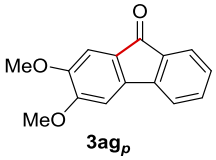
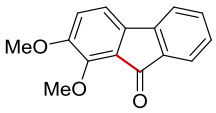
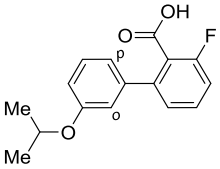
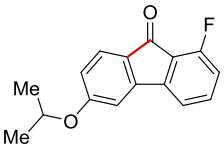
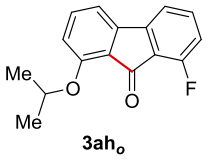
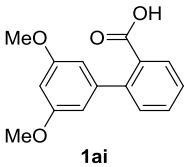
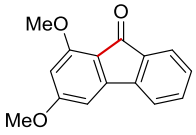
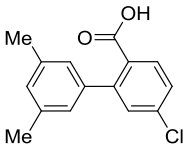
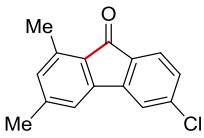
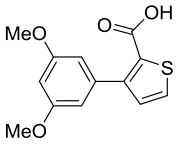
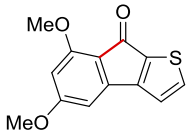
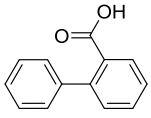
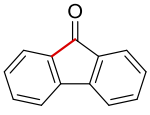
entry	carboxylic acid	product (% yield)	time (h)	reported yield (conditions)[ref]
1	 **1a**	 **3a** (97%)	2	I. 93% (PPA, DCM, reflux, 2h)[178] II. 97% (1.1 equiv trichloroacetic anhydride, 70 °C, 6 min)[179]
2	 **1b**	 **3b** (86%)	5	96% (1.1 equiv $SnCl_4$, DCM, 0 °C, 2 h)[180]
3	 **1c**	 **3c** (73%)	5	–

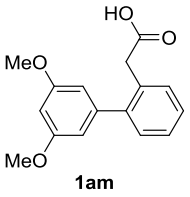
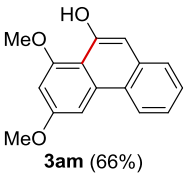
4	 **1d**	 **3d** (58%)	10	–
5	 **1e**	 **3e** (81%)	3	I. 85% (H_3PO_4, Ac_2O, 120–140 °C, 3 h)[181] II. 76% (Eaton's reagent, 100 °C, 5 min)[182] III. 62% (1.2 equiv $SnCl_2$, EtOAc, 0 °C to rt, 3.5 h)[183]
6	 **1f**	 **3f** (72%)	5	I. 72% ($SOCl_2$, 1 drop pyridine, 70 °C, 24 h)[184] II. 71% (P_2O_5, $MeSO_3H$, rt, 90 min)[185] III. 78% ($SOCl_2$, 4 drops pyridine, reflux, 8 h)[186]
7	 **1g**	 **3g** (99%)	5	54% ($AlCl_3$, rt, 12 h)[187]
8	 **1h**	 **3h** (90%)	5	–
9	 **1i**	 **3i** (70%)	5	I. 81% (H_3PO_4, P_2O_5, rt, 24 h)[188] II. 53% (1 mol% $Bi[N(SO_2CF_3)_2]$, *p*-xylene, 180 °C, 20 h)[189] III. 98% (10 mol% $Eu(OTf)_3$, 180 °C, 14 h)[112] IV. 87% (H_3PO_4, P_2O_5, 100 °C, 2 h)[190]
10	 **1j**	 **3j** (53%)	5	53% (PPA, 80 °C, 3 h)[191]

11	 **1k**	 **3k$_p$** +  **3k$_o$** (75%; 82:18)	4	–
12	 **1l**	 **3l** (92%)	3	48% (PPA, 60 °C, 2 h)[192]
13	 **1m**	 **3m$_p$** +  **3m$_o$** (96%; 64:36)	3	–
14	 **1n**	 **3n$_\alpha$** +  **3n$_\beta$** (99%; 93:7)	3	–
15	 **1o**	 **3o** (77%)	5	I. >99% (BF_3·$2CF_3CH_2OH$, DCM, rt)[193] II. 90% (1.5 equiv $POCl_3$, reflux, 30 min)[194] III. 92% (Nafion-H, *m*-dichlorobenzene, reflux, 3 h)[195]

16	 **1p**	 **3p** (72%)	5	I. 60% (PPA, 90°C, 1 h)[196] II. 96% (PPA, 90°C, 1 h)[197]
17	 **1q**	 **3q** (73%)	5	–
18	 **1r**	 **3r** (77%)	4	I. 99% (7.5 equiv $AlCl_3$, 8.5 equiv NaCl, 200 °C, 25 min)[198] II. 67% (H_2SO_4, 100 °C, 3 h)[199]
19	 **1s**	 **3s** (93%)	5	92% ($MeSO_3H$, 4 equiv P_2O_5, rt, 18 h)[200]
20	 **1t**	 **3t** (93%)	2.5	Reaction of ethyl ester of **1t** in PPA at 100 °C for 1 h gave the same yield.[201]
21	 **1u**	 **3u** (82%)	3	–
22	 **1v**	 **3v** (81%)	4	I. 70% (1.1 equiv trichloroacetic anhydride, 70 °C, 6 h)[179] II. 72% ($SnCl_4$, benzene, 0 °C, 25 min)[202]
23	 **1w**	 **3w** (59%)	6	–
24	 **1x**	 **3x** (56%)	5	80% (PCl_5, $SnCl_4$, CS_2, reflux, 35 h)[203]

25	 **1y**	 **3y** (61%)	5	–
26	 **1z**	 **3z** (72%)	5	–
27	 **1aa**	 **3aa** (68%)	5	–
28	 **1ab**	 **3ab** (72%)	5	–
29	 **1ac**	 **3ac** (14%)	16	I. 30% ($MeSO_3H$, P_2O_5, rt, 1 h)[204] II. 54% ($MeSO_3H$, P_2O_5, rt, 40 min)[205] III. 44% (HF, 30 °C, 12 h)[206]
30	 **1ad**	 **3ad** (71%)	4	I. 76% (PPA, toluene, reflux, 4 h)[207] II. 95% (PPA, toluene, reflux, 4 h)[208]
31	 **1ae**	 **3ae$_2$** +  **3ae$_7$** (78%; 85:15)	5	–
32	 **1af**	 **3af** (87%)	2.5	–

33	 **1ag**	 **3ag$_p$** +  **3ag$_o$** (93%; 98:2)	2.5	For **3ag$_p$**: 94% (7.0 equiv trifluoroacetic anhydride, $CHCl_3$, rt, 30 min)[209]
34	 **1ah**	 **3ah$_p$** +  **3ah$_o$** (99%; 76:24)	3.5	–
35	 **1ai**	 **3ai** (99%)	2.5	86% (trifluoroacetic anhydride/$CHCl_3$ (1:3), rt, 30 min)[210]
36	 **1aj**	 **3aj** (97%)	3	–
37	 **1ak**	 **3ak** (72%)	4	–
38	 **1al**	 **3al** (12%)	4	I. 100% (7.5 equiv $AlCl_3$, 8.5 equiv NaCl, 180–190 °C, 20 min)[198] II. 99% (PPA, 120 °C, 2 h)[127]

39	 **1am**	 **3am** (66%)	5	–

Mechanistic studies

The generally accepted mechanism for the Friedel–Crafts acylation is shown in Figure 12.[211-213] The mechanism of present work studied based on the experiments in Scheme 20. Porco et al. showed that a preformed HFIP ester can undergo FC cyclization reaction in the presence of K_3PO_4 at 60 °C.[214] However, when we treated HFIP ester **4a** in HFIP with 1.1 equiv of AcCl (HCl is generated in situ from the action of HFIP on AcCl[172]), **4a** was quantitatively recovered. This result suggest that **4a** is not an intermediate in the FC acylation reaction.

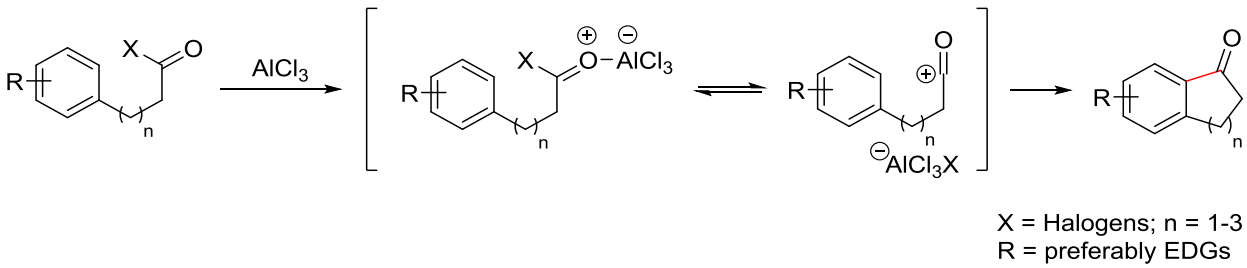
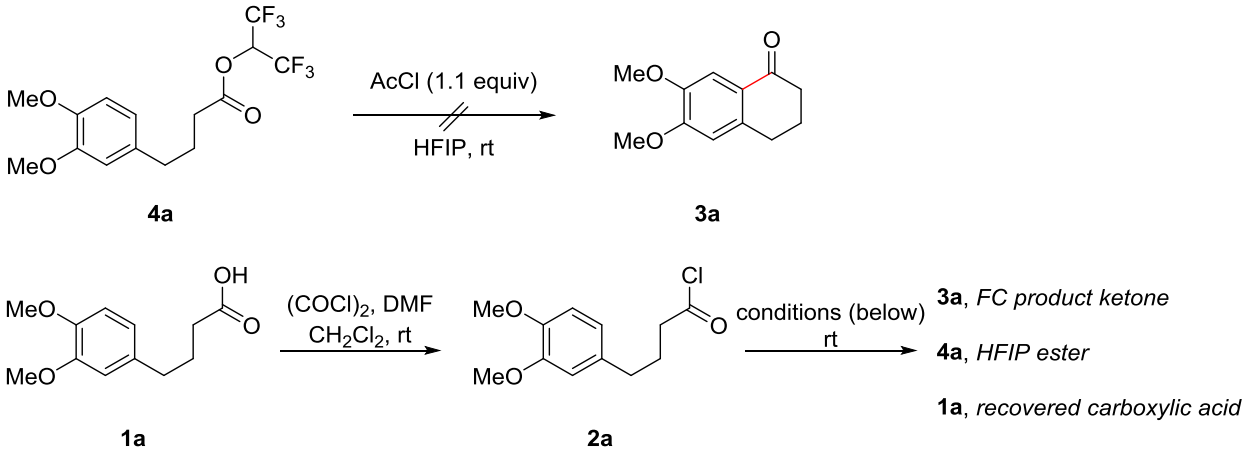


Figure 12. General mechanism of Friedel–Crafts acylation

In comparison to HFIP, when HCl was used in FC acylation in DCM, it found modestly competent but still an inferior promotor (Scheme 20). In the presence of a proton scavenger, product conversion was diminished but the reaction was not completely inhibited (even with 1.0 equiv of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), 30% of **3a** was obtained). When 2.0 equiv of pyridine (both a hydrogen bond acceptor (pK_{HB} = 1.86) and a proton scavenger[215]) was used, FC reaction did not occur but rather HFIP ester **4a** was exclusively obtained. Finally, when the

reaction was carried out with 3.0 equiv of the strong H-bond acceptor Ph_3PO and excess of HFIP (9.5 equiv), product **3a** was obtained in 96% yield. In contrast, when performed with a slight excess of Ph_3PO, the reaction was almost completely inhibited. Considering above results, hydrogen bond donor properties of HFIP seems most critical in these FC reactions.

Scheme 20. Experiments to probe mechanism



Experiments	Conditions	products		
		3a	**4a**	**1a**
Presence/absence of HFIP	HFIP (1 equiv), DCM	71%	–	–
	4.0 M HCl in dioxane (1 equiv), DCM	40%	–	44%
Addition of proton scavenger	DTBMP (0.50 equiv), DCM/HFIP (4:1)	71%	22%	–
	DTBMP (1.0 equiv), DCM/HFIP (4:1)	30%	66%	–
	pyridine (2.0 equiv), DCM/HFIP (1:1)	–	95%	–
Addition of strong H-bond acceptor	Ph_3PO (3.0 equiv), HFIP (9.5 equiv), DCM	96%	–	–
	Ph_3PO (6.0 equiv), HFIP (5.0 equiv), DCM	6%	–	73%

It has been reported that the observed effects of HFIP are due to the higher order of its aggregates rather than in its monomeric form.[216-218] Berkessel and coworkers done both theoretical and experimental studies to determine the influence of conformation and aggregation on hydrogen bond donor ability of HFIP.[175] Based on DFT analysis, they observed an substantial effect of conformation along the CO-bond of HFIP on H-bond donor ability. Both DFT and single-crystal X-ray analyses revealed that the synclinal (or even synperiplanar) confirmation of HFIP is more dominant compare to antiperiplanar conformation because in synclinal conformation HFIP exist strong H-bond donor ability. X-ray analysis also revealed the presence of H-bonded aggregates of HFIP in helical forms. In addition, they observed cooperativity in H-bond donor ability of HFIP. In other words, coordination of second and third molecule of HFIP increases H-bond donor ability of terminal hydroxyl group while no further enhancement detected for aggregation beyond the HFIP trimers.

Berkessel et al. studied the kinetics of olefin epoxidation with H_2O_2 in HFIP.[175] They found the kinetic rate order in HFIP to be 2.78 ± 0.23 when 1,2-dichlroethane was used as cosolvent. We briefly studied the kinetics of FC acylation reaction of **2a** to give product **3a** in HFIP using reactIR.

A series of FC acylation reactions were performed in different amounts of HFIP using DCM, which is inert to the FC acylation conditions, as the cosolvent. In all reactions, the total volume of the HFIP/DCM mixture was kept constant. The reactions were monitored using *in situ* ReactIR (Mettler Toledo ReactIR iC10 with silicon probe) for the disappearance of the peak at 1801 cm^{-1}, which represents the acyl chloride carbonyl group (Figure 13).

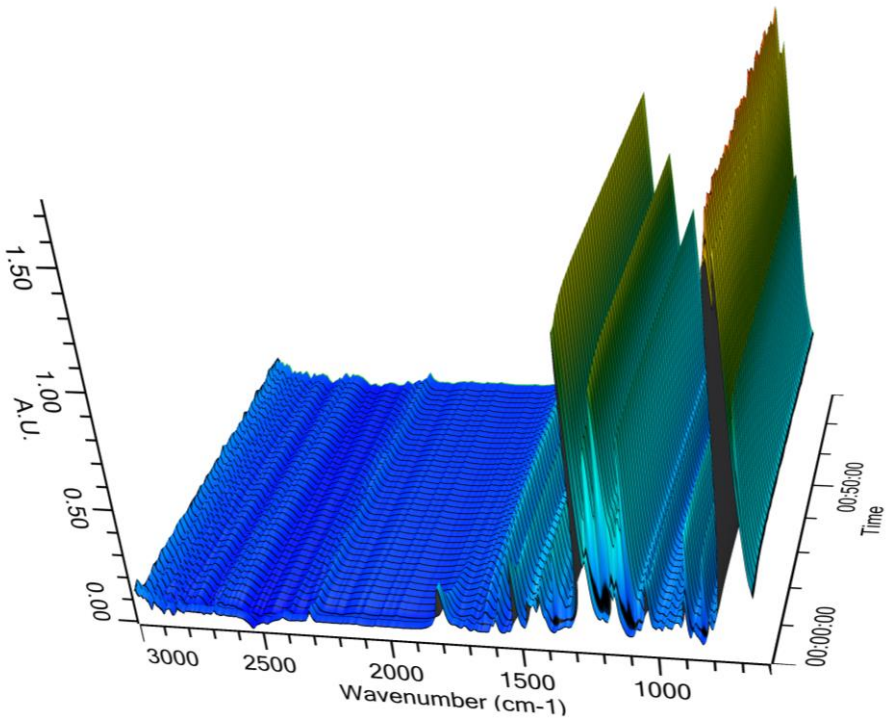
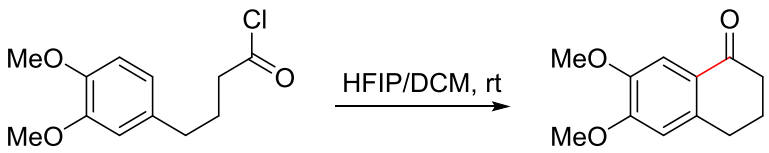


Figure 13. 3D-profile of the FC reaction of 4-(3,4-dimethoxyphenyl)butanoyl chloride (**2a**, 0.078 g, 0.300 mmol, 1.0 equiv) promoted by HFIP (0.10 mL, 0.900 mmol, 3.0 equiv) in DCM (0.90 mL) through in situ IR.

Reactions were analyzed as first-order kinetics in substrate by plotting ln[100-(%conv)/100] vs time (Figure 14a-e). The kinetic rate order in HFIP was determined by plotting reaction rates as a function of the HFIP concentrations (Figure 14f). We found a kinetic rate order of 3 in HFIP which is in accord with previously reported olefin epoxidation studies in HFIP. This also suggest involvement of more than one molecule of HFIP in the rate limiting step in FC acylation reaction.



2a **3a**

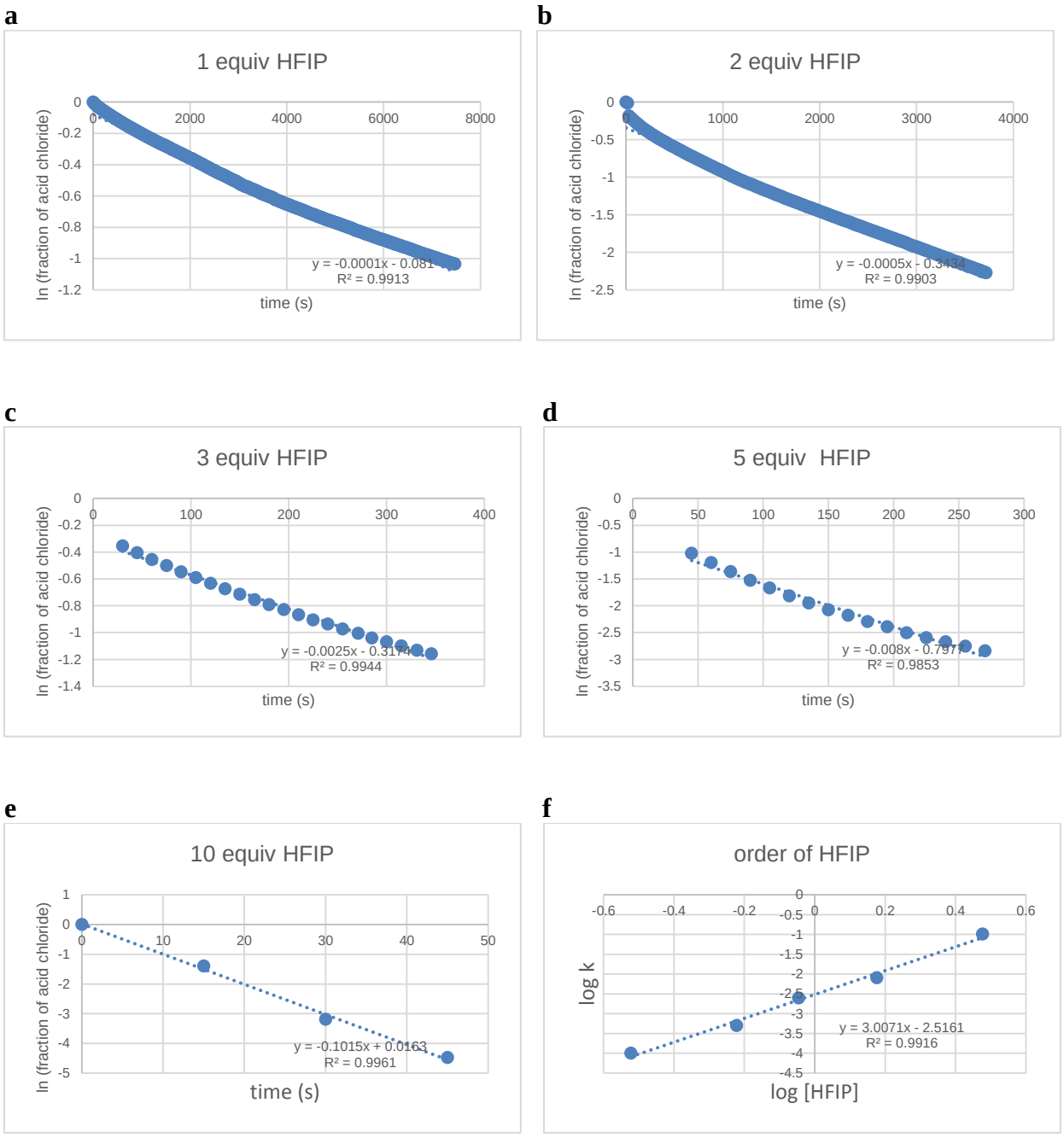
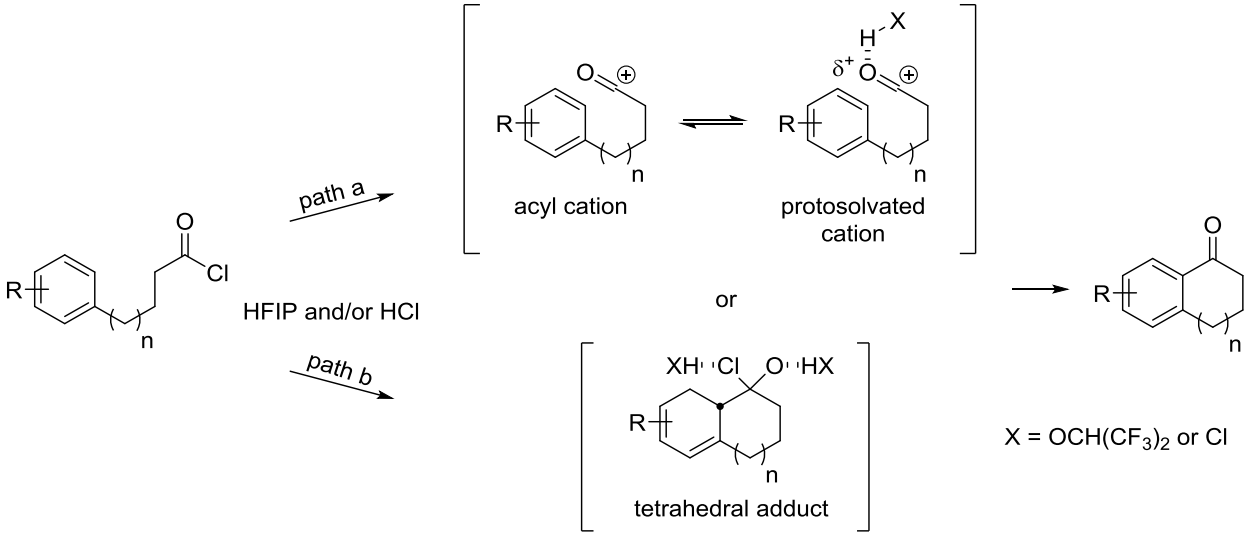


Figure 14. FC acylation of **2a** in different amount of HFIP using DCM as a cosolvent.

As mentioned earlier, HFIP ester of acid chloride is not a reactive intermediate. Thus, Scheme 21 shows plausible reaction mechanism. Path a, in agreement with traditionally believed FC acylation mechanism, HFIP could lead to the acyl cation formation.[211-213] Also acyl cation could

be protonated by either HFIP or HCl to give a kinetically superior intermediate.[219-221] In path b, aromatic ring could directly attack acyl chloride (activated through H-bonding with HFIP) to give a tetrahedral intermediate. At present, the operative pathway is not known.

Scheme 21. Plausible reaction mechanism



2.3 Conclusions

In conclusion, an efficient and metal-free intramolecular FC acylation reaction was developed. These conditions do not require aqueous workup, which is common with traditional methods, thus avoid toxic water waste generation. Our method is mild compared to previous methods that involve excess of harsh acids. Preliminary mechanistic studies indicate the involvement of more than one molecule of HFIP in rate limiting step, however further studies need to be done to figure out complete picture of mechanism.

2.4 Experimental Section

General information. Reactions were performed under an inert atmosphere (argon or nitrogen) in oven-dried glassware. All chemicals were used as received from commercial source without further purification. TLC was performed using commercial glass-backed silica plates (250

microns) with an organic binder. Visualization was accomplished using UV light or aqueous $KMnO_4$ by heating. Purification was achieved by flash chromatography on a CombiFlash Rf (automated flash chromatography) system. IR spectra were acquired as thin films or solids. All NMR spectra (^1H, ^{13}C, DEPT, COSY, NOESY, HMBC, and HSQC) were acquired on either a 400 MHz or a 500 MHz instrument. Chemical shifts are reported in parts per million (ppm) and are referenced to the center line of the solvent (δ 7.26, 2.50, and 5.32 ppm with respect to $CDCl_3$, DMSO-d_6, and CD_2Cl_2 for ^1H NMR and δ 77.23, 39.52, and 55.84 ppm with respect to $CDCl_3$, DMSO-d_6, and $CD_2Cl_2$for ^{13}C NMR, respectively). Coupling constants are given in Hertz (Hz). HRMS data were collected with an electrospray ion source (ESI). Melting points were determined on an automated melting point apparatus and are uncorrected. Melting points were determined in open capillary tubes using an automated melting point apparatus and are uncorrected.

Dr. Hashim Motiwala performed all experiments in Table 3 (screening of reaction conditions), Table 4 (screening of alternative reagents), and Scheme 13 (experiments to probe mechanism). Compounds **3a**, **3d**, **3j**, **3k**, **3l**, **3m**, **3n**, **3r**, **3t**, **3u**, **3v**, **3w**, **3ad**, **3ag**, **3ah**, **3ai**, **3aj**, **3ak**, and **3al** were synthesized by him. He performed scale up reaction of **3a.**

General Procedure A for Solvent Screening (Table 5):

Procedure (Step 1 → Synthesis of Acid Chloride): To a solution of acid **1a** (67.3 mg, 0.300 mmol, 1.0 equiv) in anhydrous DCM (1.5 mL) in a flame-dried N_2-flushed 2-dram vial at rt under N_2 blanket was added a small drop (using a 21G needle) of *N*,*N*-dimethylformamide (DMF). Then oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) was added dropwise (gas evolution was observed; the cap was opened for a while under N_2 blanket to release the pressure) and the reaction mixture was stirred at rt for 30 min. Reaction mixture was concentrated under N_2 using sample

concentrator and the residue obtained was dried under vacuum for ca. 15 min. The crude acid chloride **2a** was used as such for the Step 2.

Procedure (Step 2 → Friedel–Crafts Acylation; For Entries 1, 9, and 10):

To the same 2-dram vial containing the crude acid chloride intermediate **2a** at rt was added a specified volume of HFIP quickly and the vial was capped immediately. The resultant reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated under N_2 and the resulting residue was dissolved in a minimum quantity of DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 4 g normal phase silica flash column (0–40% EtOAc/hexanes over 20 min) afforded **3a** as a colorless solid following concentration and drying under vacuum.

Procedure (Step 2 → Friedel–Crafts Acylation; For Entries 2–8):

To the same 2-dram vial containing the crude acid chloride intermediate **2a** at rt was added an appropriate volume of anhydrous solvent (DCM, acetonitrile, nitromethane, trifluorotoluene, or THF) followed by a quick addition of a specified volume of HFIP (total volume of solvents was 1.5 mL) and the vial was immediately capped. The resultant reaction mixture was stirred at rt for 2–6 h. Reaction mixture was concentrated under N_2 and the resulting residue was dissolved in a minimum quantity of DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 4 g normal phase silica flash column (0–40% EtOAc/hexanes over 20 min) afforded **3a** as a colorless solid (in case of pure product) or a creamish-orange solid (in case of impure product) following concentration and drying under vacuum.

General Procedure B for Comparison with Alternative Reagents (Table 6):

Procedure (Step 1 → Synthesis of Acid Chloride): To a solution of acid **1a** (22.4 mg, 0.100 mmol, 1.0 equiv) in anhydrous DCM (0.50 mL) in a flame-dried N_2-flushed 1-dram vial at rt under N_2 blanket was added a small drop (using a 21G needle) of DMF. Then oxalyl chloride (17 μL, 0.200 mmol, 2.0 equiv) was added dropwise (gas evolution was observed; the cap was opened for a while under N_2 blanket to release the pressure) and the reaction mixture was stirred at rt for 15 min. Reaction mixture was concentrated under N_2 using a sample concentrator and the residue obtained was dried under vacuum for ca. 15 min. The crude acid chloride **2a** was used as such for the Step 2.

Procedure (Step 2 → Friedel–Crafts Acylation; For Entries 1–6): To the same 1-dram vial containing the crude acid chloride intermediate **2a** at rt was added anhydrous DCM (0.50 mL) followed by the addition of a reagent (0.50 mmol, 5.0 equiv) and the resultant reaction mixture was stirred at rt for 4 or 6 h. The reaction mixture was concentrated under N_2 and the resulting residue was dried under vacuum. The residue was dissolved in $CDCl_3$ (0.60 mL) followed by the addition of nitromethane (10 μL) as an internal standard. The mixture was homogenized and the $CDCl_3$ suspension was filtered through a cotton plug into a NMR tube (if a solution was obtained, no filtration was carried out). ^{1}H NMR was recorded and the NMR yield was determined where product was formed.

NMR yield was calculated using the following equation:

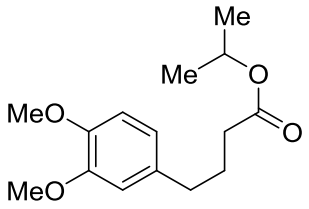
$$W_p = \frac{A_p}{A_{is}} \times \frac{N_{is}}{N_p} \times \frac{MW_p}{MW_{is}} \times W_{is}$$

Subscripts "p" and "is" refer to the product and internal standard.

A = area under the peak or absolute integral for a signal, N = number of protons, MW = molecular weight, and W = weight or amount used.

Procedure (Step 2 → Friedel–Crafts Acylation; For Entries 7–12):

To the same 1-dram vial containing the crude acid chloride intermediate **2a** at rt was added a reagent (0.50 mL) and the resultant reaction mixture was stirred at rt for 45 min or 4 h. The reaction mixture was concentrated under N_2 or Genevac (for entry 10) and the resulting residue was dried under vacuum. The residue was dissolved in CDCl3 (0.60 mL) followed by the adddition of nitromethane (10 μL) as an internal standard. The mixture was homogenized and the solution was transferred to a NMR tube. ^{1}H NMR was recorded and the NMR yield was determined where product was formed.



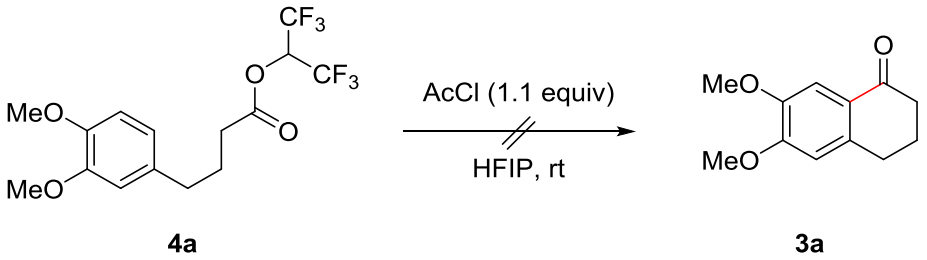
4b

Isopropyl 4-(3,4-dimethoxyphenyl)butanoate (4b):

In case of entry 12, the residue obtained after drying was dissolved in a minimum quantity of DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 4 g normal phase silica flash column (0–15% EtOAc/hexanes over 15 min) afforded **4b** (24.5 mg, 92%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80–6.78 (m, 1H), 6.72–6.70 (m, 2H), 5.01 (hept, *J* = 6.3 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.92 (p, *J* = 7.5 Hz, 2H), 1.23 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.2, 149.1, 147.5, 134.4, 120.5, 112.1, 111.5, 67.7, 56.1, 56.0, 34.9, 34.2, 27.0, 22.1 (2C); IR

(neat) 1725, 1514 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{23}O_4$ $[M + H]^+$: 267.1596, found: 267.1605.

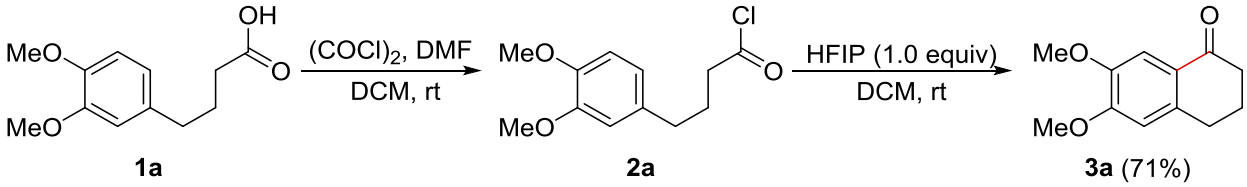
Experimental Procedures for Scheme 20 (Control Experiments to Probe the Hydrogen Bonding Mechanism):



4a **3a**

a. Reaction of 4a with acetyl chloride in HFIP:

To a solution of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(3,4-dimethoxyphenyl)butanoate **4a** (37.3 mg, 0.100 mmol, 1.0 equiv) in HFIP (0.25 mL) in a flame-dried N_2-flushed 1-dram vial at rt was added acetyl chloride (7.79 μL, 0.110 mmol, 1.1 equiv) and the resulting reaction mixture was stirred at rt for 1.5 h. No reaction was observed and crude ^{1}H NMR only showed peaks corresponding to **4a**.

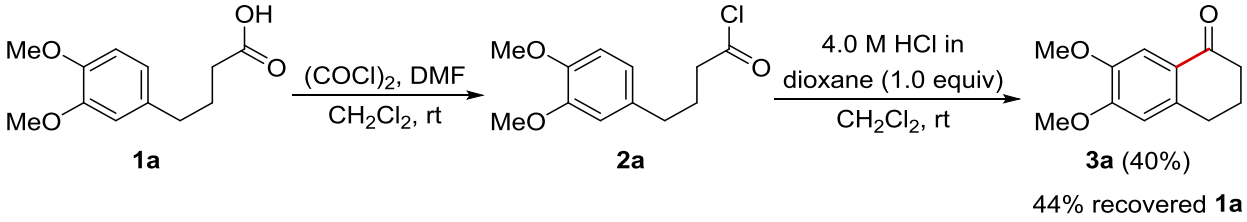


1a **2a** **3a** (71%)

b. Reaction of 2a with 1 equiv of HFIP:

Procedure (Step 1): Following the general procedure **A** for Step 1, 4-(3,4-dimethoxyphenyl)butanoic acid **1a** (67.3 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(3,4-dimethoxyphenyl)butanoyl chloride **2a** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min.

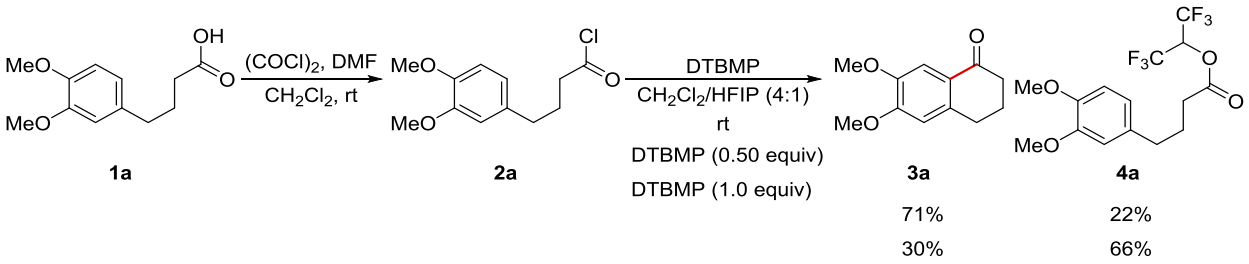
Procedure (Step 2): To a solution of the crude acid chloride **2a** in anhydrous DCM (1.5 mL) in a capped vial at rt was added HFIP (31.6 μL, 0.300 mmol, 1.0 equiv) using a microsyringe and the resultant reaction mixture was stirred at rt for 1.5 h. Reaction mixture was concentrated under N_2 and the resulting residue was dissolved in a minimum quantity of DCM and loaded on to silica gel in a sample cartridge. Purification on a Combiflash purification system using a 4 g normal phase silica flash column (0–40% EtOAc/hexanes over 20 min) afforded **3a** (43.8 mg, 71%) as a colorless solid.



c. Reaction of 2a with added HCl in the absence of HFIP:

Procedure (Step 1): Following the general procedure **A** for Step 1, 4-(3,4-dimethoxyphenyl)butanoic acid **1a** (67.3 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(3,4-dimethoxyphenyl)butanoyl chloride **2a** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min.

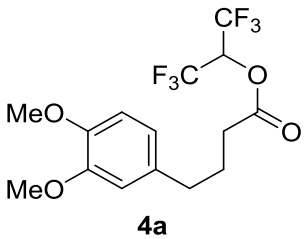
Procedure (Step 2): To a solution of the crude acid chloride **2a** in anhydrous DCM (1.5 mL) at rt was added HCl (4.0 M solution in dioxane) (75.0 μL, 0.300 mmol, 1.0 equiv) and the resultant reaction mixture was stirred at rt for 1.5 h. Reaction mixture was partially concentrated under N_2 and the resulting solution including the rinsings in DCM was loaded on to silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g normal phase silica flash column (0–60% EtOAc/hexanes over 30 min) afforded **3a** (26.0 mg, 42%) as a colorless solid. Acid **1a** was recovered in 44% yield (29.9 mg) as a colorless solid.



d. Reaction of 2a in the presence of a proton scavenger, DTBMP:

Procedure (Step 1): Following the general procedure **A** for Step 1, 4-(3,4-dimethoxyphenyl)butanoic acid **1a** (67.3 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(3,4-dimethoxyphenyl)butanoyl chloride **2a** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min.

Procedure (Step 2): To the same 2-dram vial containing the crude acid chloride intermediate **2a** at rt was added anhydrous DCM (1.2 mL) followed by the addition of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP; 61.6 mg, 0.300 mmol, 1.0 equiv). To the resulting suspension was added HFIP (0.30 mL) and the reaction mixture was stirred at rt for 1.5 h. Reaction mixture was concentrated under N_2 and the residue obtained was redissolved in DCM and loaded on to silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g normal phase silica flash column (0–30% EtOAc/hexanes over 30 min) afforded **3a** as an off-white solid (18.5 mg, 30%) and **4a** as a colorless oil (74.5 mg, 66%). In a similar way as described above for Step-2, when 0.50 equiv DTBMP (30.8 mg, 0.150 mmol) was used, **3a** (44.2 mg, 71%) was isolated as an off-white solid and **4a** (25.0 mg, 22%) was obtained as a colorless oil.

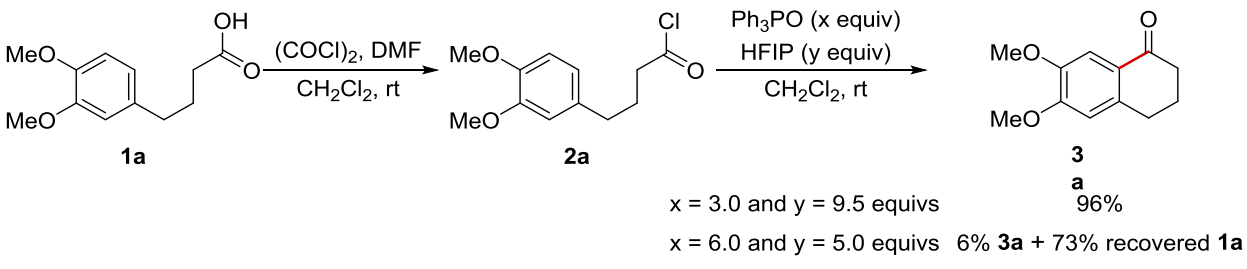


4a

e. Reaction of 2a in the presence of pyridine:

Procedure (Step 1): Following the general procedure **B** for Step 1, 4-(3,4-dimethoxyphenyl)butanoic acid **1a** (22.4 mg, 0.100 mmol, 1.0 equiv) was converted to 4-(3,4-dimethoxyphenyl)butanoyl chloride **2a** using oxalyl chloride (16.9 μL, 0.200 mmol, 2.0 equiv) in 15 min.

Procedure (Step 2): To the same 1-dram vial containing the crude acid chloride intermediate **2a** at rt was added anhydrous DCM (0.25 mL) followed by the addition of pyridine (16.2 μL, 0.200 mmol, 2.0 equiv). To the resulting solution was added HFIP (0.25 mL) and the reaction mixture was stirred at rt for 4 h. Reaction mixture was concentrated under N_2 and the resulting residue was dissolved in a minimum quantity of DCM and loaded on to silica gel in a sample cartridge. Purification on a Combiflash purification system using a 4 g normal phase silica flash column (0–15% EtOAc/hexanes over 15 min) afforded 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(3,4-dimethoxyphenyl)butanoate **4a** (35.4 mg, 95%) as a colorless oil. TLC (30% EtOAc/hexanes) R_f = 0.76; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (d, *J* = 7.9 Hz, 1H), 6.68–6.72 (m, 2H), 5.79 (hept, *J* = 6.2 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.52 (t, *J* = 7.4 Hz, 2H), 2.00 (p, *J* = 7.4 Hz, 2H); $_{13}$C NMR (101 MHz, $CDCl_3$): δ 170.4, 149.3, 147.8, 133.4, 120.5, 116.4–124.9 (m, 2C), 112.0, 111.6, 66.6 (p, *J* = 34.7 Hz, 1C), 56.1, 56.0, 34.5, 32.6, 26.5; IR (neat) 1779, 1516, 1196, 1106 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{16}F_6O_4$ [M + H]$^+$: 375.1031, found: 375.1022.



f. Reaction of 2a in the presence of a strong hydrogen bond acceptor, Ph3PO:

Procedure (Step 1):

Following the general procedure **A** for Step 1, 4-(3,4-dimethoxyphenyl)butanoic acid **1a** (67.3 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(3,4-dimethoxyphenyl)butanoyl chloride **2a** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min.

Procedure (Step 2 for 9.5 Equiv of HFIP) To the same 2-dram vial containing the crude acid chloride intermediate **2a** at rt was added anhydrous DCM (1.2 mL) followed by the addition of triphenylphosphine oxide (Ph_3PO; 251 mg, 0.900 mmol, 3.0 equiv). To the resulting solution was added HFIP (0.300 mL, 2.85 mmol, 9.5 equiv) and the reaction mixture was stirred at rt for 1.5 h. Reaction mixture was concentrated under N_2 and the residue obtained was dissolved in DCM and loaded on to silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g normal phase silica flash column (0–40% EtOAc/hexanes over 20 min) afforded **3a** (59.3 mg, 96%) as a very pale yellow solid.

Procedure (Step 2 for 5.0 Equiv of HFIP) To the same 2-dram vial containing the crude acid chloride intermediate **2a** at rt was added anhydrous DCM (1.34 mL) followed by the addition of Ph_3PO (501 mg, 1.80 mmol, 6.0 equiv). To the resulting solution was added HFIP (0.158 mL, 1.50 mmol, 5.0 equiv) and the reaction mixture was stirred at rt for 1.5 h. Reaction mixture was concentrated under N_2 and the residue obtained was dissolved in DCM and loaded on to silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g normal phase silica flash column (0–60% EtOAc/hexanes over 30 min) afforded **3a** (4.00 mg, 6%) as a colorless solid. Acid **1a** was recovered in 73% yield (49.3 mg; corrected yield based on ca. 93% purity) as a colorless solid.

General procedure for the kinetic analysis of the FC acylation of 2a (Figure 14):

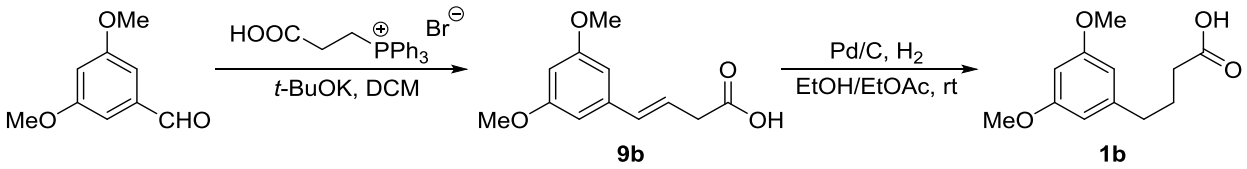
4-(3,4-Dimethoxyphenyl)butanoyl chloride (2a):

To a solution of 4-(3,4-dimethoxyphenyl)butanoic acid (0.5 g, 2.2 mmol, 1.0 equiv) in anhydrous DCM (5 mL) rt under N_2 blanket was added DMF (2 drops). Then oxalyl chloride (0.28 mL, 3.3 mmol, 1.5 equiv) was added dropwise (gas evolution was observed; the cap was opened for a while under N_2 blanket to release the pressure) and the reaction mixture was stirred at rt for 30 mins. Reaction mixture was concentrated and the residue obtained was dried under vacuum for 1 h. To the crude pentane (3 mL) was added and resulting mixture was sonicated for 5 mins. Then the mixture was kept in freezer for 2 h. The clear pentane layer was removed and the residue was washed 3 times with fresh pentane. The remaining residue was dried under vacuum to give pure acid chloride (0.408 g, 75%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.0 Hz, 1H), 6.72 – 6.69 (m, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 2.88 (t, *J* = 7.2 Hz, 2H), 2.63 (t, *J* = 7.5 Hz, 2H), 2.02 (p, *J* = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 149.1, 147.7, 133.0, 120.5, 111.8, 111.5, 56.1, 56.0, 46.3, 34.0, 26.9.

To a solution of 4-(3,4-dimethoxyphenyl)butanoyl chloride (**2a**, 0.078 g, 0.300 mmol, 1.0 equiv) in DCM, was added HFIP (1, 2, 3, 5, or 10 equiv). The combined volume of DCM and HFIP was kept 1 mL in each case. The reaction mixture was stirred at rt and monitored by reactIR until the complete consumption of starting acyl chloride.

entry	HFIP (equiv)	HFIP (mL)	DCM (mL)
1	1	0.03	0.97
2	2	0.06	0.94
3	3	0.10	0.90
4	5	0.16	0.84
5	10	0.32	0.68

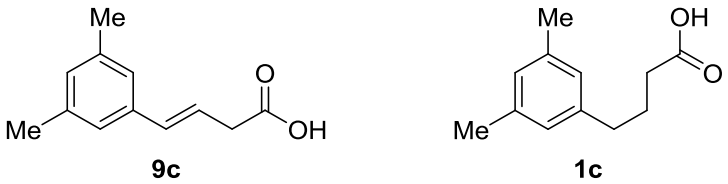
Syntheses of compounds:



4-(3,5-Dimethoxyphenyl)butanoic acid (1b):[222]

To a cooled solution of (2-carboxyethyl)triphenylphosphonium bromide (1.50 g, 3.60 mmol, 1.2 equiv) in DCM (5.0 mL) at 0 °C under N_2 atmosphere was added 3,5-dimethoxybenzaldehyde (0.500 g, 3.00 mmol, 1.0 equiv). To the resulting mixture, potassium *tert*-butoxide (0.840 g, 7.50 mmol, 2.5 equiv) was added portion wise and the reaction mixture was allowed to stir at rt for 12 h. The reaction was quenched with water and DCM layer was separated and discarded. The aqueous layer was acidified with 1 M HCl to pH 1 and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with water (10 mL × 1), brine (10 mL × 1), dried over Na_2SO_4, and concentrated. Purification on a Combiflash purification system using a silica flash column (70:30 hexanes/EtOAc) afforded (*E*)-4-(3,5-dimethoxyphenyl)but-3-enoic acid **9b**[223] (0.153 g, 23%) as a colorless solid.

To a solution of compound **9b** (0.152 g, 0.680 mmol) in EtOAc (2.0 mL) under Ar atmosphere was added 10% of Pd/C (15.0 mg, 10 wt%) followed by EtOH (6.0 mL). The reaction mixture was evacuated under vacuum and flushed with H_2 gas (3 cycles) and was continued to stir under H_2 atmosphere at rt for 1 h. The reaction mixture was filtered through a pad of Celite followed ringing with EtOH. Solvent evaporation afforded **1b** (0.142 g, 93%) as a colorless solid.

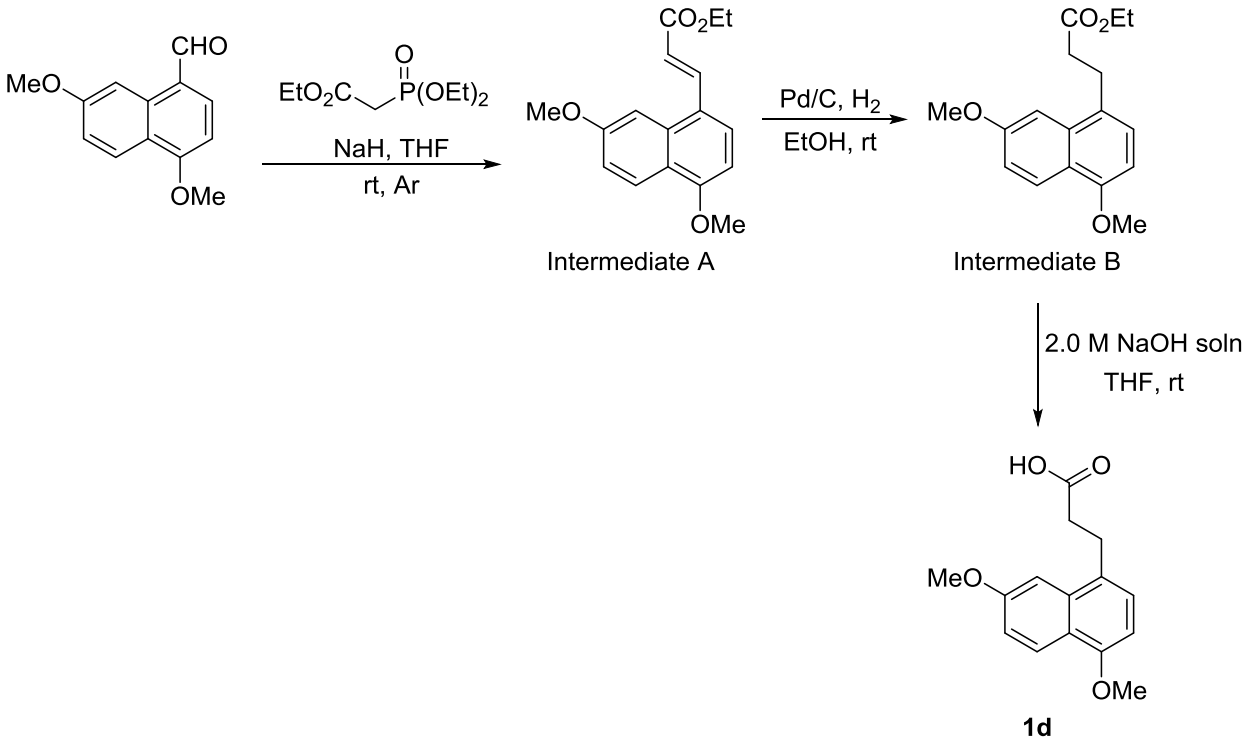


4-(3,5-Dimethylphenyl)butanoic acid (1c):

Following the procedure described for compound **1b**, 3,5-dimethylbenzaldehyde (1.00 g, 7.45 mmol, 1.0 equiv) was reacted with (2-carboxyethyl)triphenylphosphonium bromide (3.71 g, 8.94 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (2.09 g, 18.6 mmol, 2.5 equiv) to afford (*E*)-4-(3,5- dimethylphenyl)but-3-enoic acid **9c** (0.475 g, 33%) as a colorless oil. TLC (50% EtOAc/hexanes) R_f = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (dd, *J* = 1.7, 0.9 Hz, 2H), 6.93–6.84 (m, 1H), 6.46 (dt, *J* = 15.8, 1.4 Hz, 1H), 6.25 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.28 (dd, *J* = 7.1, 1.4 Hz, 2H), 2.30 (d, *J* = 0.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 138.2 (2C), 136.7, 134.3, 129.6, 124.4 (2C), 120.5, 38.1, 21.4 (2C); IR (neat) 3700–2300, 1755 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}O_2$ $[M + H]^+$: 191.1072, found: 191.1043.

Compound **9c** (0.420 g, 2.21 mmol) was then reduced with Pd/C (0.0420 g, 10 wt%) under H_2 atmosphere in EtOH to afford **1c** (0.400 g, 94%) as a colorless solid. Mp 61–62 °C; TLC (50% EtOAc/hexanes) R_f = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, *J* = 1.8 Hz, 1H), 6.82–6.77 (m, 2H), 2.65–2.55 (m, 2H), 2.38 (t, *J* = 7.5 Hz, 2H), 2.29 (d, *J* = 0.8 Hz, 6H), 1.95 (p, *J* = 7.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.0, 141.2, 138.0 (2C), 127.8, 126.5 (2C), 35.0, 33.6, 26.4, 21.4 (2C); IR (neat) 3400–2300, 1687 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{17}O_2$ $[M + H]^+$: 193.1229, found: 193.1213.

3-(4,7-Dimethoxynaphthalen-1-yl)propanoic acid (1d):



Following a modification of the literature procedure,[224] 3-(4,7-dimethoxynaphthalen-1-yl)propanoic acid **1d** was prepared from 4,7-dimethoxy-1-naphthaldehyde in the following manner:

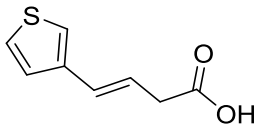
To a suspension of sodium hydride (60% dispersion in mineral oil) (72.0 mg, 1.80 mmol, 1.2 equiv; washed with hexanes once) in anhydrous THF (4.0 mL) in a flame-dried RBF at rt under Ar was added a solution of triethyl phosphonoacetate (403 mg, 1.80 mmol, 1.2 equiv) in anhydrous THF (1.5 mL, including the washings) slowly over 5 min (effervescence was observed). The resulting solution was stirred at rt for 30 min. A solution of 4,7-dimethoxy-1-naphthaldehyde (324 mg, 1.50 mmol, 1.0 equiv) in anhydrous THF (2.5 mL, including the washings) was added slowly to the reaction mixture over 15 min and the stirring was continued at rt for 2 h. Some unreacted

4,7-dimethoxy-1-naphthaldehyde was observed by TLC, so additional sodium hydride (24.0 mg, 0.600 mmol, 0.40 equiv) and triethyl phosphonoacetate (101 mg, 0.450 mmol, 0.30 equiv) was directly added into the reaction mixture and the reaction mixture was continued to stir at rt for another 1 h. Reaction mixture was concentrated, diluted with water (30 mL), and extracted with ether (25 mL × 2). The combined organic layers were washed with brine (30 mL × 1), dried over Na_2SO_4, and concentrated to afford 429 mg of crude intermediate **A** [(*E*)-ethyl 3-(4,7-dimethoxynaphthalen-1-yl)acrylate] as a semisolid residue, which was used as such for the next hydrogenation step.

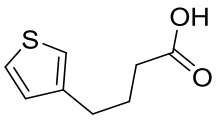
To a solution of the crude Intermediate **A** (429 mg) in ethanol (8.0 mL) under N_2 was added 10% of Pd/C (43.1 mg, 0.405 mmol, 10 wt%). The resulting suspension was evacuated under vacuum and flushed with H_2 twice and was continued to stir under H_2 atmosphere at rt for 3.5 h. The reaction mixture was filtered through a Celite bed followed by ether rinsings. Solvent evaporation afforded crude Intermediate **B** [(ethyl 3-(4,7-dimethoxynaphthalen-1-yl)propanoate] as an oily residue, which was used as such for the next saponification step.

To a solution of Intermediate **B** in THF (4.0 mL) at rt in an open flask was added sodium hydroxide (2.0 M solution in deionized water; 6.00 mL, 12.00 mmol, 8.0 equiv) and the resulting biphasic solution was stirred at rt for 12 h. Reaction mixture was acidified with 1.0 M aqueous HCl with stirring until acidic (pH = 1) and the resulting aqueous suspension was extracted with DCM (25 mL × 2). The combined organic layers were dried over Na_2SO_4 and concentrated to give a cream-orange solid. The solid was suspended in DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–5% MeOH/DCM over 25 min) afforded **1d** (347 mg, 89% over 3 steps) as a cream solid. Mp 148.5–150 °C; TLC (30% EtOAc/hexanes) R_f = 0.21; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.16 (brs, 1H),

8.10 (d, *J* = 9.2 Hz, 1H), 7.27 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.15 (dd, *J* = 9.2, 2.5 Hz, 1H), 6.73 (d, *J* = 7.9 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.17 (t, *J* = 7.5 Hz, 2H), 2.61 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.0, 157.8, 153.8, 133.4, 127.4, 126.4, 123.8, 120.1, 116.6, 102.7, 101.9, 55.3, 55.1, 34.4, 27.1; IR (neat) 3350–2350, 1710, 1692 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{17}O_4$ $[M + H]^+$: 261.1127, found: 261.1118.



9f

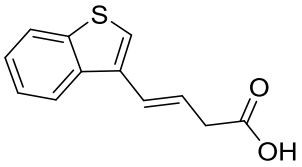


1f

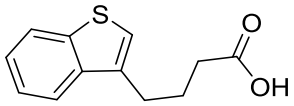
4-(Thiophen-3-yl)butanoic acid (1f): Following the procedure described for compound **1b**, 3-thiophenecarboxaldehyde (1.00 g, 8.92 mmol, 1.0 equiv) was reacted with (2-carboxyethyl)triphenylphosphonium bromide (4.44 g, 10.7 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (2.50 g, 22.3 mmol, 2.5 equiv) to afford (*E*)-4-(thiophen-3- yl)but-3-enoic acid **9f** (0.375 g, 26%) as a golden brown solid. Mp 90–92 °C; TLC (50% EtOAc/hexanes) R_f = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (m, 1H), 7.21 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.14 (dd, *J* = 3.0, 1.3 Hz, 1H), 6.53 (dt, *J* = 15.9, 1.5 Hz, 1H), 6.13 (dt, *J* = 15.8, 7.2 Hz, 1H), 3.26 (dd, *J* = 7.1, 1.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 139.4, 128.4, 126.2, 125.1, 122.3, 120.8, S17 38.0; IR (neat) 3400–2100, 1705 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_8H_9O_2S$ $[M + H]^+$: 169.0323, found: 169.0309.

Compound **9f** (0.357 g, 2.12 mmol) was then reduced with Pd/C (0.0357 g, 10 wt%) under H_2 atmosphere in EtOH to afford **1f** (0.360 g, 99%) as a colorless oil. TLC (50% EtOAc/hexanes) R_f = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.24 (m, 1H), 6.95 (ddt, *J* = 8.0, 4.3, 2.2 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 2.49–2.26 (m, 2H), 1.97 (p, *J* = 7.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ

179.1, 141.6, 128.2, 125.7, 120.7, 33.4, 29.5, 25.6; IR (neat) 3500–2300, 1700 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_8H_{11}O_2S$ $[M + H]^+$: 171.0480, found: 171.0463.



9g

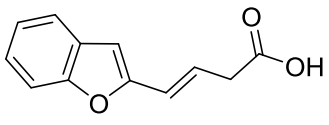


1g

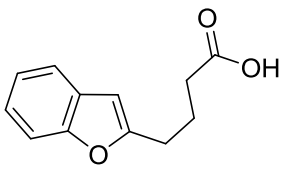
4-(Benzo[*b*]thiophen-3-yl)butanoic acid (1g):[225]

Following the procedure described for compound **1b**, thianaphthene-3-carboxaldehyde (1.00 g, 6.16 mmol, 1.0 equiv) was reacted with (2-carboxyethyl)triphenylphosphonium bromide (3.07 g, 7.39 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (1.73 g, 15.4 mmol, 2.5 equiv) to afford (*E*)-4- (benzo[*b*]thiophen-3-yl)but-3-enoic acid **9g** (0.550 g, 41%) as an orange solid. Mp 93–95 °C; TLC (50% EtOAc/hexanes) R_f = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.81 (m, 2H), 7.44 (s, 1H), 7.43–7.33 (m, 2H), 6.80 (dq, *J* = 15.9, 1.3 Hz, 1H), 6.37 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.38 (dd, *J* = 7.2, 1.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 140.6, 137.7, 133.5, 126.5, 124.6, 124.4, 123.0, 122.8, 122.5, 122.1, 38.2; IR (neat) 3300–2200, 1681 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{11}O_2S$ $[M + H]^+$: 219.0480, found: 219.0465.

Compound **9g** (0.424 g, 1.94 mmol) was then reduced with Pd/C (0.0424 g, 10 wt%) under H_2 atmosphere in EtOH to afford **1g** (0.354 g, 83%) as a colorless solid.



9h

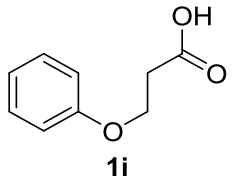


1h

4-(Benzofuran-2-yl)butanoic acid (1h):[226]

Following the procedure described for compound **1b**, 2-benzofurancarboxaldehyde (1.00 g, 6.84 mmol, 1.0 equiv) were reacted with (2-carboxyethyl)triphenylphosphonium bromide (3.41 g, 8.21 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (1.92 g, 17.1 mmol, 2.5 equiv) to afford (*E*)-4- (benzofuran-2-yl)but-3-enoic acid **9h** (0.450 g, 33%) as a yellow solid. Mp 110–112 °C; TLC (50% EtOAc/hexanes) R_f = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (ddd, *J* = 7.6, 1.4, 0.7 Hz, 1H), 7.46–7.41 (m, 1H), 7.28–7.41 (m, 1H), 7.19 (td, *J* = 7.5, 1.0 Hz, 1H), 6.60–6.44 (m, 3H), 3.35 (d, *J* = 6.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 155.0, 154.0, 128.9, 124.8, 123.1, 123.0, 122.7, 121.1, 111.1, 104.7, 37.8; IR (neat) 3400–2100, 1687 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_9O_3$ $[M - H]^-$: 201.0552, found: 201.0556.

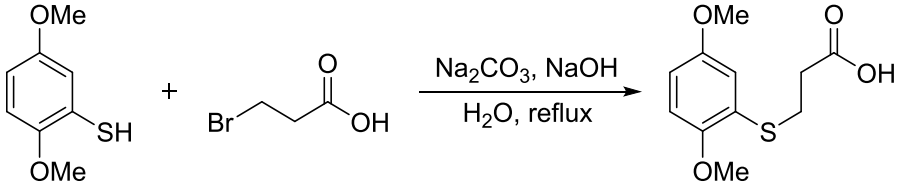
Compound **9h** (0.300 g, 1.48 mmol) was then reduced with Pd/C (0.0300 g, 10 wt%) under H_2 atmosphere in EtOH to afford **1h** (0.235 g, 78%) as a colorless solid. Mp 76–78 °C; TLC (50% EtOAc/hexanes) R_f = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.46 (m, 1H), 7.44–7.39 (m, 1H), 7.25– 7.12 (m, 2H), 6.43 (d, *J* = 0.9 Hz, 1H), 2.86 (t, *J* = 7.1 Hz, 2H), 2.47 (t, *J* = 7.4 Hz, 2H), 2.10 (p, *J* = 7.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 158.1, 154.9, 128.9, 123.5, 122.7, 120.5, 110.9, 102.8, 33.2, 27.8, 22.9; IR (neat) 3400–2300, 1692 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{11}O_3$ $[M - H]^-$: 203.0708, found: 203.0709.



1i

3-Phenoxypropanoic acid (1i):[227]

To a solution of phenol (0.500 g, 5.30 mmol, 1.0 equiv) and 3-bromopropionic acid (0.810 mg, 5.30 mmol, 1.0 equiv) in DMF (5.0 mL) at rt under Ar atmosphere was added Cs_2CO_3 (3.46 g, 10.6 mmol, 2.0 equiv) and the resulting suspension was continued to stir at rt for 15 h. The reaction mixture was quenched with 1 M HCl to pH 1 and the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with water (10 mL × 1), brine once, dried over Na_2SO_4, and concentrated. Purification on a Combiflash purification system using a silica flash column (80:20 hexanes/EtOAc) afforded **1i** (0.148 g, 17%) as a colorless solid.

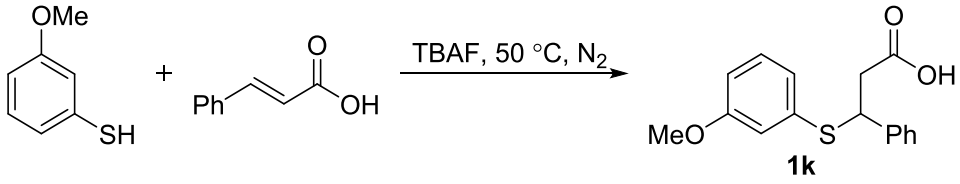


1j

3-((2,5-Dimethoxyphenyl)thio)propanoic acid (1j):

Following a reported procedure,[192] to a suspension of 3-bromopropanoic acid (225 mg, 1.47 mmol, 1.05 equiv) in deionized water (5.0 mL) at rt was added anhydrous sodium carbonate (163 mg, 1.54 mmol, 1.1 equiv) slowly. After the effervescence ceased, the clear solution was cooled to ca. 5–10 °C and this cold solution was added to a turbid solution of 2,5-dimethoxybenzenethiol (238 mg, 1.40 mmol, 1.0 equiv) in sodium hydroxide (84.0 mg, 2.10 mmol, 1.5 equiv) and deionized water (3.0 mL) at rt in a microwave vial (10–20 mL capacity). The vial was sealed and the resulting turbid solution was stirred at refluxing temperature (100–105 °C) for 1.5 h. Reaction mixture was cooled to rt and extracted with EtOAc (30 mL × 1) and the EtOAc layer was discarded. The aqueous layer was acidified with 2 M aqueous HCl solution (10 mL) and the resulting turbid solution was extrated with DCM (25 mL × 3). The combined organic layers were washed with brine (30 mL × 1), dried over Na_2SO_4, and concentrated. The oil obtained was redissolved in DCM

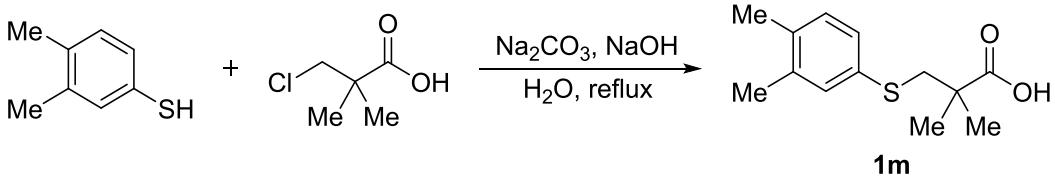
and loaded on to silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–50% EtOAc/hexanes over 25 min) afforded **1j** (257 mg, 76%) as a colorless crystalline solid. Mp 100–102 °C; TLC (50% EtOAc/hexanes) R_f = 0.37; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.84 (brs, 1H), 6.91 (d, *J* = 2.9 Hz, 1H), 6.80 (d, *J* = 8.9 Hz, 1H), 6.74 (dd, *J* = 8.9, 2.9 Hz, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.14 (t, *J* = 7.4 Hz, 2H), 2.68 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.2, 153.8, 152.4, 124.1, 117.1, 112.4, 111.8, 56.4, 55.9, 34.2, 27.1; IR (neat) 3670–2380, 1707 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{11}H_{15}O_4S$ $[M + H]^+$: 243.0691, found: 243.0666.



3-((3-Methoxyphenyl)thio)-3-phenylpropanoic acid (1k):

Following a modification of the reported procedure,[228] to a mixture of 3-methoxybenzenethiol (421 mg, 3.00 mmol, 2.0 equiv) and *trans*-cinnamic acid (223 mg, 1.50 mmol, 1.0 equiv) in a dried N_2-flushed 2-dram vial at rt was added 1.0 M solution of tetrabutylammonium fluoride in THF (0.751 mL, 0.751 mmol, 0.50 equiv) . The vial was capped and the resulting suspension was stirred at 50 °C under N_2 for 6 h (most of the THF had evaporated within 2 h). The reaction mixture was dissolved in a minimum quantity of DCM and loaded on to silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–30% EtOAc/hexanes over 30 min) afforded **1k** (272 mg, 63%) as a colorless solid. Mp 81–83 °C; TLC (25% EtOAc/hexanes, run twice) R_f = 0.32; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 (brs, 1H), 7.26–7.17 (complex, 5H), 7.11 (m, 1H), 6.88 (m, 1H), 6.76–6.72 (m, 2H), 4.59 (dd, *J* = 8.0, 7.2 Hz, 1H),

3.65 (s, 3H), 2.94 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 159.8, 140.4, 134.7, 129.8, 128.7 (2C), 127.9 (3C), 125.6, 118.3, 114.4, 55.4, 48.7, 40.8; IR (neat) 3500–2400, 1707 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{17}O_3S$ $[M + H]^+$: 289.0898, found: 289.0881.

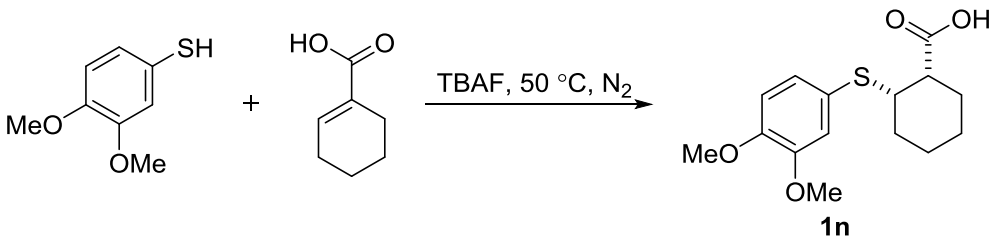


1m

3-((3,4-Dimethylphenyl)thio)-2,2-dimethylpropanoic acid (1m):

Following a reported procedure,[192] to a suspension of 3-chloro-2,2-dimethylpropanoic acid (215 mg, 1.58 mmol, 1.05 equiv) in deionized water (5.0 mL) at rt was added anhydrous Na_2CO_3 (175 mg, 1.65 mmol, 1.1 equiv) slowly. After the effervescence ceased, the clear solution was cooled to ca. 5–10 °C and this cold solution was added to a turbid solution of 3,4-dimethylbenzenethiol (207 mg, 1.50 mmol, 1.0 equiv) in sodium hydroxide (90.0 mg, 2.25 mmol, 1.5 equiv) and deionized water (3.0 mL) at rt in a big microwave vial. The vial was sealed and the resulting turbid solution was stirred at refluxing temperature (100–105 °C) for 1.5 h. The reaction mixture was cooled to rt and acidified with 2 M aqueous HCl solution (10 mL). The resulting suspension was extracted with DCM (25 mL × 3). The combined organic layers were washed with brine (30 mL × 1), dried over Na_2SO_4, and concentrated. The oil obtained was dissolved in hexanes containing a small amount of DCM and the solution was loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–20% EtOAc/hexanes over 40 min) afforded **1m** (330 mg, 92%) as an almost colorless crystalline solid. Mp 70–71.5 °C; TLC (30% EtOAc/hexanes) R_f = 0.51; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.66 (brs, 1H), 7.20 (s, 1H), 7.15 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 3.16 (s, 2H), 2.23 (d, *J*

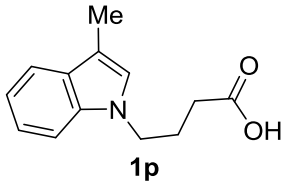
= 4.0 Hz, 6H), 1.31 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.5, 137.4, 135.3, 133.7, 132.1, 130.3, 128.4, 45.4, 44.2, 24.8 (2C), 19.9, 19.5; IR (neat) 3400–2300, 1693 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{19}O_2S$ $[M + H]^+$: 239.1106, found: 239.1080.



Rel-(1*S*,2*S*)-2-((3,4-Dimethoxyphenyl)thio)cyclohexanecarboxylic acid (1n):

Following a modification of the reported procedure,[228] to a mixture of 3,4-dimethoxybenzenethiol (511 mg, 3.00 mmol, 2.0 equiv) and 1-cyclohexene-1-carboxylic acid (189.2 mg, 1.500 mmol, 1.0 equiv) in a dried N_2-flushed 2-dram vial at rt was added 1.0 M solution of tetrabutylammonium fluoride in THF (0.750 mL, 0.750 mmol, 0.50 equiv). The vial was capped and the resulting solution was stirred at 50 °C under N_2 for 1 h. Reaction mixture was dissolved in a minimum quantity of DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–2% MeOH/DCM over 40 min) afforded impure **1n** as a colorless solid. Recrystallization of the solid from DCM/hexanes mixture (solid was dissolved in a minimum quantity of DCM and then hexanes was added until the solution became slightly turbid) afforded pure **1n** (275 mg, 62%) as a colorless crystalline solid after filtration and drying under vacuum. Mp 111.5–113.5 °C; TLC (2% MeOH/DCM) R_f = 0.22; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.63 (brs, 1H), 7.06 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.59 (m, 1H), 2.79 (m, 1H), 2.00 (m, 1H), 1.88–1.76 (complex, 4H), 1.69 (m, 1H), 1.50 (m, 1H), 1.36–1.24 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.6, 149.2, 149.1, 126.8, 126.5, 117.1, 111.6, 56.13, 56.08, 51.0, 46.8, 31.4, 24.6, 24.3,

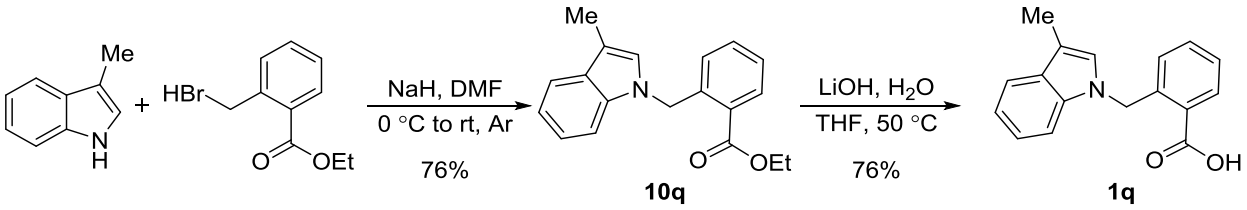
21.8; IR (neat) 3450–2350, 1703 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{21}O_4S$ $[M + H]^+$: 297.1161, found: 297.1141.



1p

4-(3-Methyl-1*H*-indol-1-yl)butanoic acid (1p):[197]

Following the literature procedure,[197] 3-methylindole (0.200 g, 1.52 mmol, 1.0 equiv) was reacted with γ-butyrolactone (0.262 g, 3.05 mmol, 2.0 equiv) in the presence of sodium hydride (60% dispersion in mineral oil) (0.122 g, 3.05 mmol, 2.0 equiv) to afford **1p** (0.200 g, 61%) as a brown solid. Mp 82–84 °C; TLC (20% EtOAc/hexanes) R_f = 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.30 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.21 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.86 (d, *J* = 1.1 Hz, 1H), 4.16 (t, *J* = 6.8 Hz, 2H), 2.40–2.29 (m, 5H), 2.15 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 136.4, 129.0, 125.5, 121.7, 119.3, 118.8, 110.8, 109.2, 45.0, 30.9, 25.4, 9.7; IR (neat) 3300–2200, 1702 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{16}NO_2$ $[M + H]^+$: 218.1181, found: 218.1188.

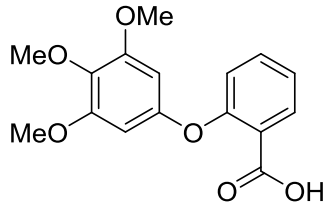


2-((3-Methyl-1*H*-indol-1-yl)methyl)benzoic acid (1q): To a cooled solution of 3-methylindole (0.200 g, 1.52 mmol, 1.0 equiv) in DMF (5.0 mL) at 0 °C under Ar atmosphere was added sodium hydride (60% dispersion in mineral oil) (0.0730 g, 1.83 mmol, 1.2 equiv). After stirring for 10 min at 0 °C, ethyl 2-(bromomethyl)benzoate (0.440 g, 1.83 mmol, 1.2 equiv) was added and the

reaction mixture was continued to stir at 0 °C for 15 min. The reaction mixture was warmed to rt and continued to stir at rt for 1 h. The reaction was quenched with water and the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with water (10 mL × 1), brine once, dried over Na_2SO_4, and concentrated. Purification on a Combiflash purification system using a silica flash column (90:10 hexanes/EtOAc) afforded ethyl 2-((3-methyl-1*H*-indol-1-yl)methyl)benzoate **10q** (0.340 g, 76%) as a colorless oil. TLC (10% EtOAc/hexanes) R_f = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–7.98 (m, 1H), 7.66–7.56 (m, 1H), 7.33–7.27 (m, 2H), 7.22–7.05 (m, 3H), 6.90 (d, *J* = 1.1 Hz, 1H), 6.56–6.46 (m, 1H), 5.72 (d, *J* = 0.8 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.37 (d, *J* = 1.1 Hz, 3H), 1.43 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 140.5, 136.9, 132.9, 131.0, 129.0, 128.3, 127.2, 127.2, 126.4, 121.8, 119.1, 119.0, 111.2, 109.7, 61.3, 48.4, 14.5, 9.8; IR (neat) 1712 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{20}NO_2$ $[M + H]^+$: 294.1494, found: 294.1463.

To a solution of **10q** (0.330 g, 1.12 mmol, 1.0 equiv) in THF (6.0 mL) was added a suspension of LiOH (0.108 g, 4.50 mmol, 4.0 equiv) in water (2.0 mL) and the resulting mixture was stirred at 50 °C for 24 h. The reaction mixture was acidified with 1 M HCl to pH 1 and the mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with water (10 mL × 1), brine once, dried over Na_2SO_4, and concentrated. Purification on a Combiflash purification system using a silica flash column (95:5 DCM/MeOH) afforded **1q** (0.225 g, 76%) as a colorless solid. Mp 166–168 °C; TLC (10% EtOAc/hexanes) R_f = 0.10; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dt, *J* = 6.9, 1.4 Hz, 1H), 7.69–7.57 (m, 1H), 7.44–7.30 (m, 2H), 7.22–7.07 (m, 3H), 6.96–6.87 (m, 1H), 6.51 (dd, *J* = 7.2, 2.0 Hz, 1H), 5.78 (s, 2H), 2.38 (t, *J* = 1.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 141.8, 136.9, 134.1, 132.1, 129.0, 127.37, 127.35, 126.5, 126.3, 121.9, 119.2,

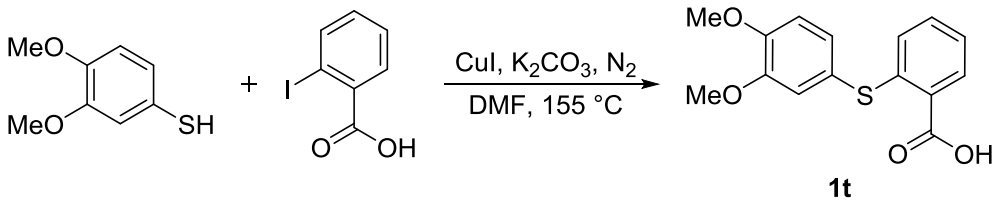
119.1, 111.3, 109.7, 48.6, 9.8; IR (neat) 3200–2000, 1679 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{16}NO_2$ $[M + H]^+$: 266.1181, found: 266.1185.



1s

2-(3,4,5-Trimethoxyphenoxy)benzoic acid (**1s**):

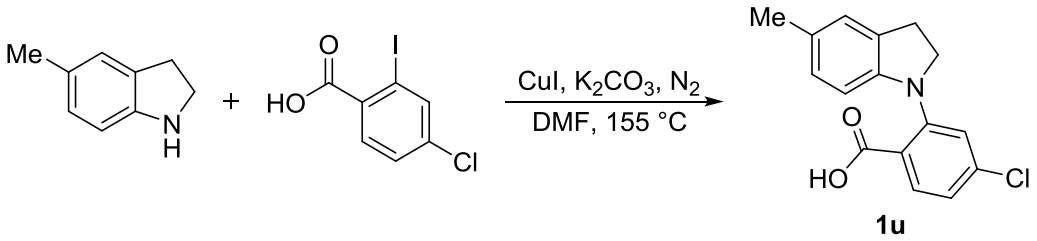
Following a modification of the reported procedure,[229] to a solution of 2-bromobenzoic acid (0.500 g, 2.48 mmol, 1.0 equiv) in DMF (15 mL) were added 3,4,5-trimethoxyphenol (0.916 g, 4.97 mmol, 2.0 equiv), 1,8-diazabicyclo[5.4.0]undec-7-ene (1.14 g, 7.46 mmol, 3.0 equiv), pyridine (40.0 μL), copper (0) (20.0 mg), and copper iodide (20.0 mg) in succession and the resulting mixture was refluxed for 2 h. The reaction mixture was acidified with 1 M HCl to pH 1 and the mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with water (10 mL × 1), brine once, dried over Na_2SO_4, and concentrated. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **1s** (0.350 g, 46%) as a colorless solid. Mp 144–145 °C; TLC (50% EtOAc/hexanes) R_f = 0.10; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.49 (ddd, *J* = 8.3, 7.3, 1.8 Hz, 1H), 7.23–7.16 (m, 1H), 6.90 (dd, *J* = 8.4, 0.9 Hz, 1H), 6.35 (s, 2H), 3.84 (s, 3H), 3.81 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 157.6, 154.1, 151.2, 151.1, 135.3, 134.7, 133.2, 123.3, 119.8, 117.9, 97.8 (2C), 61.0, 56.2 (2C); IR (neat) 3400–2200, 1692, 1670, 1596 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{17}O_6$ $[M + H]^+$: 305.1025, found: 305.0996.



1t

2-((3,4-Dimethoxyphenyl)thio)benzoic acid (1t):[230]

Following a slight modification of the reported procedure,[231] to a solution of 3,4-dimethoxybenzenethiol (255 mg, 1.50 mmol, 1.0 equiv) and 2-iodobenzoic acid (372 mg, 1.50 mmol, 1.0 equiv) in anhydrous DMF (2.5 mL) in a flame-dried N_2-flushed microwave vial at rt was added potassium carbonate (207 mg, 1.50 mmol, 1.0 equiv) and copper(I) iodide (57.1 mg, 0.300 mmol, 0.20 equiv). The vial was sealed with a N_2 balloon inserted into a septum and the resulting suspension was stirred at 155 °C for 18 h (effervescence was observed and hood lights were kept off). Reaction mixture was quenched with 1.0 M aqueous HCl (10 mL), diluted with water (20 mL), and extracted with DCM (25 mL × 3). The combined organic layers were washed with water (60 mL × 3), brine (60 mL × 1), dried over Na_2SO_4, and concentrated. The residue obtained was suspended in DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–5% MeOH/DCM over 50 min) afforded impure **1t** as a brownish-grey solid. Trituration of the solid with ether twice and with ether containing few drops of DCM once afforded pure **1t** (238 mg, 55%) as an off-white solid after filtration and drying under vacuum. Mp 216–220 °C (lit.[230] Mp 215–217 °C); TLC (5% MeOH/DCM) R_f = 0.37; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.16 (brs, 1H), 7.91 (dd, J = 7.8, 1.5 Hz, 1H), 7.35 (td, J = 8.1, 7.4, 1.6 Hz, 1H), 7.08–7.18 (m, 4H), 6.69 (d, J = 8.1 Hz, 1H), 3.82 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.4, 150.1, 149.6, 143.5, 132.4, 130.9, 128.9, 126.6, 126.0, 124.1, 122.0, 118.5, 112.8, 55.7, 55.6; IR (neat) 3350–2200, 1668 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{15}O_4S$ $[M + H]^+$: 291.0691, found: 291.0675.

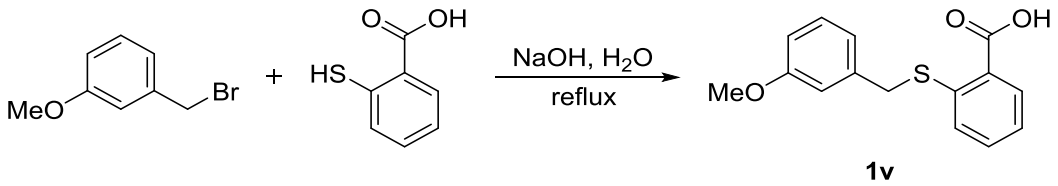


1u

4-Chloro-2-(5-methylindolin-1-yl)benzoic acid (1u):

Following a slight modification of the reported procedure,[231] to a solution of 5-methylindoline (266 mg, 2.00 mmol, 1.0 equiv) and 4-chloro-2-iodobenzoic acid (565 mg, 2.00 mmol, 1.0 equiv) in anhydrous DMF (2.5 mL) in a flame-dried N_2-flushed microwave vial at rt was added potassium carbonate (276 mg, 2.00 mmol, 1.0 equiv) and copper(I) iodide (76.0 mg, 0.400 mmol, 0.20 equiv). The vial was sealed with a N_2 balloon inserted into a septum and the resulting suspension was stirred at 155 °C for 16 h (effervescence was observed and hood lights were kept off). Reaction mixture was quenched with 1.0 M aqueous HCl (10 mL), diluted with water (20 mL), and extracted with DCM (25 mL × 3). The combined organic layers were washed with water (50 mL × 3), brine (50 mL × 1), dried over Na_2SO_4, and concentrated. The residue obtained was redissolved in DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 24 g silica flash column (0–2% MeOH/DCM over 40 min) afforded **1u** as an orange oily solid, which showed some decomposition to a corresponding oxidized indole byproduct in $CDCl_3$ overtime at rt. Repurification of an impure sample of **1u** on a Combiflash purification system using a 12 g silica flash column (100% DCM over 40 min) afforded a slightly impure (ca. 94% pure) **1u** (195 mg, 34%; contaminated with ca. 6% of the corresponding indole byproduct) as a yellowish-orange solid. Mp 131–139 °C; TLC (4% MeOH/DCM) R_f = 0.53; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.21 (brs, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 7.41 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.32 (d, *J* = 2.0 Hz, 1H), 7.12 (s, 1H), 6.93 (m, 1H), 6.38 (d, *J* = 8.0 Hz, 1H), 3.74 (apparent t, *J* = 7.6 Hz, 2H), 3.22 (t, *J* =

7.9 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 149.3, 146.6, 140.6, 133.6, 133.4, 132.2, 128.5, 128.4, 126.1, 126.0, 125.5, 113.2, 59.4, 29.4, 21.0; IR (neat) 3400–2200, 1721, 1688 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{15}ClNO_2$ $[M + H]^+$: 288.0791, found: 288.0784.

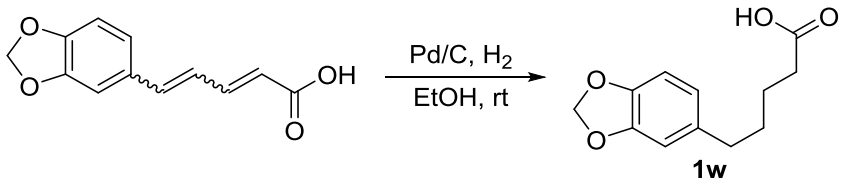


1v

2-((3-Methoxybenzyl)thio)benzoic acid (1v):

Following a modification of the reported procedure,[192] to a turbid solution of 2-mercaptobenzoic acid (200 mg, 1.30 mmol, 1.0 equiv) and sodium hydroxide (114 mg, 2.85 mmol, 2.2 equiv) in deionized water (5.0 mL) in a microwave vial at rt was added 3-methoxybenzyl bromide (274 mg, 1.36 mmol, 1.05 equiv). The vial was sealed and the turbid biphasic solution was stirred at refluxing temperature (100–105 °C) for 1.5 h. Reaction mixture was cooled to rt and extracted with EtOAc (15 mL × 1) and the EtOAc layer was discarded. The aqueous layer was acidified with 2 M aqueous HCl solution (10 mL) and the resulting turbid solution was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (30 mL × 1), dried over Na_2SO_4, and concentrated. The solid obtained was suspended in DCM with few drops of MeOH and loaded on to silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–10% MeOH/DCM over 50 min) afforded **1v** (313 mg, 88%) as a colorless fluffy solid. Mp 196–199 °C (lit.[202] mp: 199–201 °C); TLC (3% MeOH/DCM) R_f = 0.45; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.04 (s, 1H), 7.88 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.52–7.47 (m, 2H), 7.26–7.19 (m, 2H), 7.01–6.99 (m, 2H), 6.84 (m, 1H), 4.17 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.4, 159.3, 141.3, 138.2, 132.4, 130.9, 129.5, 127.6, 125.7, 124.0, 121.4, 114.8,

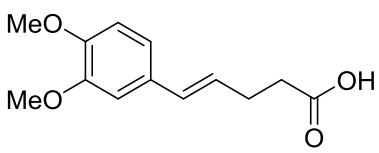
112.6, 55.0, 35.7; IR (neat) 3400–2350, 1685 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{15}O_3S$ $[M + H]^+$: 275.0742, found: 275.0742.



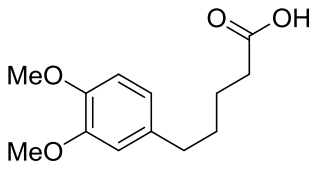
1w

5-(1,3-Benzodioxol-5-yl)pentanoic acid (1w):[232]

To a suspension of 5-(1,3-benzodioxol-5-yl)-2,4-pentadienoic acid (218 mg, 1.00 mmol, 1.0 equiv) in ethanol (5.0 mL) in an oven-dried 25 mL under N_2 was added Pd/C (10 wt%) (21.3 mg, 0.200 mmol, 0.20 equiv). The resulting suspension was evacuated under vacuum and flushed with H_2 twice and was continued to stir under H_2 atmosphere at rt for 5 h. Reaction mixture was concentrated and the residue obtained was diluted with DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–30% EtOAc/hexanes over 30 min) afforded **1w** (203 mg, 91%) as a colorless crystalline solid. Mp 95–97 °C; TLC (30% EtOAc/hexanes, run twice) R_f = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.71 (brs, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 1.5 Hz, 1H), 6.62 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.92 (s, 2H), 2.56 (t, *J* = 7.1 Hz, 2H), 2.37 (t, *J* = 7.0 Hz, 2H), 1.65 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.2, 147.8, 145.8, 136.0, 121.3, 109.0, 108.3, 100.9, 35.4, 34.1, 31.2, 24.3; IR (neat) 3300–2400, 1702 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{13}O_4$ $[M – H]^–$: 221.0814, found: 221.0828.



9x

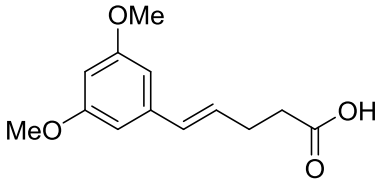


1x

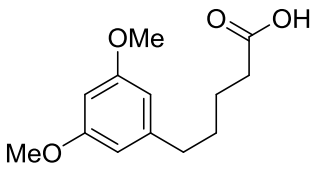
5-(3,4-Dimethoxyphenyl)pentanoic acid (1x):[233]

Following the procedure described for compound **1b**, 3,4-dimethoxylbenzaldehyde (1.00 g, 6.02 mmol, 1.0 equiv) was reacted with (2-carboxypropyl)triphenylphosphonium bromide (3.10 g, 7.22 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (1.69 g, 15.0 mmol, 2.5 equiv) to afford (*E*)-5-(3,4- dimethoxyphenyl)pent-4-enoic acid **9x** (0.615 g, 43%) as a colorless solid. Mp 114–116 °C; TLC (50% EtOAc/hexanes) R_f = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95–6.85 (m, 2H), 6.80 (d, *J* = 8.2 Hz, 1H), 6.39 (d, *J* = 15.5 Hz, 1H), 6.16–6.01 (m, 1H), 3.88 (d, *J* = 9.6 Hz, 6H), 2.54 (d, *J* = 0.7 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 149.2, 148.7, 131.0, 130.6, 126.2, 119.3, 111.4, 108.9, 56.1, 56.0, 33.9, 28.0; IR (neat) 2934, 1719, 1695, 1512 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}O_4$ $[M + H]^+$: 237.1127, found: 237.1106.

Compound **9x** (0.600 g, 2.54 mmol) was then reduced with Pd/C (0.0600 g, 10 wt%) under H_2 atmosphere in EtOH to afford **1x** (0.530 g, 88%) as a colorless solid.



9y



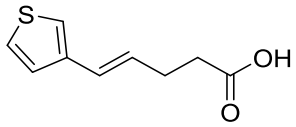
1y

5-(3,5-Dimethoxyphenyl)pentanoic acid (1y):[234]

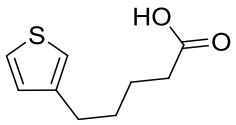
Following the procedure described for compound **1b**, 3,5-dimethoxylbenzaldehyde (0.500 g, 3.01 mmol, 1.0 equiv) was reacted with (2-carboxypropyl)triphenylphosphonium bromide (1.55 g, 3.61 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (0.844 g, 7.52 mmol, 2.5 equiv) to afford (*E*)-5-(3,5- dimethoxyphenyl)pent-4-enoic acid **9y** (0.370 g, 52%) as a colorless solid. Mp 104–106 °C; TLC (50% EtOAc/hexanes) R_f = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (d, *J* = 2.3

Hz, 2H), 6.42–6.33 (m, 2H), 6.25–6.15 (m, 1H), 3.79 (s, 6H), 2.61–2.47 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 161.1 (2C), 139.5, 131.3, 128.7, 104.4 (2C), 99.7, 55.5 (2C), 33.8, 28.0; IR (neat) 3300–2100, 1701, 1579 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}O_4$ $[M + H]^+$: 237.1127, found: 237.1098.

Compound **9y** (0.300 g, 1.27 mmol) was then reduced with Pd/C (0.0300 g, 10 wt%) under H_2 atmosphere in EtOH to afford **1y** (0.295 g, 98%) as a colorless solid.



9z

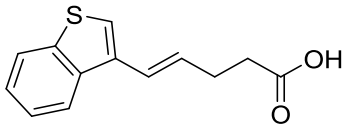


1z

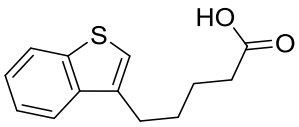
5-(Thiophen-3-yl)pentanoic acid (1z):[235]

Following the procedure described for compound **1b**, 3-thiophenecarboxaldehyde (1.00 g, 8.92 mmol, 1.0 equiv) was reacted with (2-carboxypropyl)triphenylphosphonium bromide (4.59 g, 10.7 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (2.50 g, 22.3 mmol, 2.5 equiv) to afford (*E*)-5-(thiophen-3- yl)pent-4-enoic acid **9z**[236] (1.01 g, 62%) as a brown solid.

Compound **9z** (0.657 g, 3.95 mmol) was then reduced with Pd/C (0.0657 g, 10 wt%) under H_2 atmosphere in EtOH to afford **1z** (0.320 g, 44%) as a colorless solid.



9aa

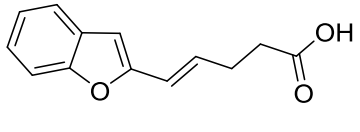


1aa

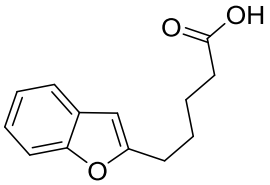
5-(Benzo[*b*]thiophen-3-yl)pentanoic acid (1aa):

Following the procedure described for compound **1b**, thianaphthene-3-carboxaldehyde (1.00 g, 6.16 mmol, 1.0 equiv) was reacted with (2-carboxypropyl)triphenylphosphonium bromide (3.17 g, 7.39 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (1.73 g, 15.4 mmol, 2.5 equiv) to afford (*E*)-5- (benzo[*b*]thiophen-3-yl)pent-4-enoic acid **9aa** (0.750 g, 52%) as a colorless solid. Mp 97–98 °C; TLC (50% EtOAc/hexanes) R_f = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.81 (m, 2H), 7.45–7.30 (m, 3H), 6.72 (dd, *J* = 15.9, 1.2 Hz, 1H), 6.34–6.21 (m, 1H), 2.67–2.55 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.3, 140.6, 137.9, 134.1, 130.1, 124.5, 124.3, 123.7, 123.0, 122.1, 121.4, 33.8, 28.4; IR (neat) 3300– 2100, 1701 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{11}O_2S$ $[M – H]^–$: 231.0480, found: 231.0489.

Compound **9aa** (0.300 g, 1.29 mmol) was then reduced with Pd/C (0.0300 g, 10 wt%) under H_2 atmosphere in EtOH to afford **1aa** (0.300 g, 99%) as a colorless solid. Mp 99–100 °C; TLC (20% EtOAc/hexanes) R_f = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.80 (m, 1H), 7.79–7.69 (m, 1H), 7.45– 7.30 (m, 2H), 7.10 (d, *J* = 1.1 Hz, 1H), 2.95–2.78 (m, 2H), 2.43 (t, *J* = 6.9 Hz, 2H), 1.80 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 140.7, 139.1, 136.5, 124.3, 124.0, 123.0, 121.7, 121.3, 33.9, 28.7, 28.4, 24.7; IR (neat) 3200–2200, 1699, 1687 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}O_2S$ $[M – H]^–$: 233.0636, found: 233.0644.



9ab

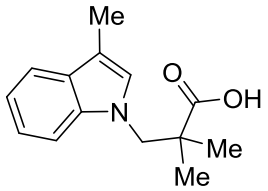


1ab

5-(Benzofuran-2-yl)pentanoic acid (1ab):

Following the procedure described for compound **1b**, 2-benzofurancarboxaldehyde (1.00 g, 6.84 mmol, 1.0 equiv) was reacted with (2-carboxypropyl)triphenylphosphonium bromide (3.53 g, 8.21 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (1.92 g, 17.1 mmol, 2.5 equiv) to afford (*E*)-5- (benzofuran-2-yl)pent-4-enoic acid **9ab** (0.950 g, 64%) as a colorless solid. Mp 106–108 °C; TLC (50% EtOAc/hexanes) R_f = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.48 (m, 1H), 7.42 (dq, *J* = 8.2, 0.9 Hz, 1H), 7.26–7.16 (m, 2H), 6.54–6.32 (m, 3H), 2.60 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 154.8, 154.6, 130.6, 129.1, 124.4, 122.9, 120.9, 120.1, 111.0, 103.8, 33.5, 27.9; IR (neat) 3300–2100, 1697 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}O_3$ $[M + H]^+$: 217.0865, found: 217.0835.

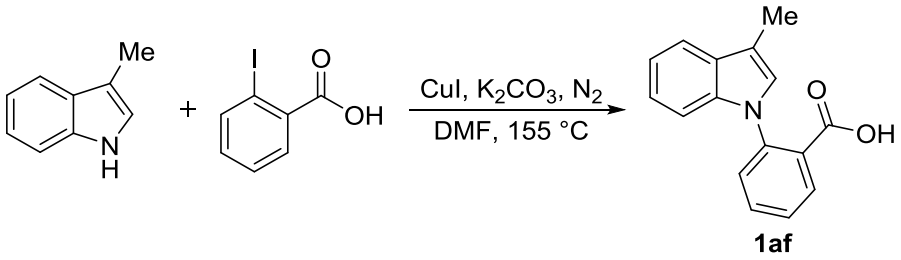
Compound **9ab** (0.300 g, 1.39 mmol) was then reduced with Pd/C (0.0300 g, 10 wt%) under H_2 atmosphere in EtOH to afford **1ab** (0.150 g, 50%) as a colorless solid. Mp 124–126 °C; TLC (20% EtOAc/hexanes) R_f = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.15 (brs, 1H), 7.52–7.45 (m, 1H), 7.43–7.38 (m, 1H), 7.24–7.15 (m, 2H), 6.40 (d, *J* = 1.0 Hz, 1H), 2.88–2.73 (m, 2H), 2.42 (t, *J* = 7.1 Hz, 2H), 1.89– 1.67 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.6, 158.9, 154.8, 129.0, 123.3, 122.6, 120.4, 110.9, 102.3, 33.7, 28.2, 27.2, 24.3; IR (neat) 3300–2100, 1705 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_3$ $[M + H]^+$: 219.1021, found: 219.0990.



1ae

2,2-Dimethyl-3-(3-methyl-1*H*-indol-1-yl)propanoic acid (1ae):

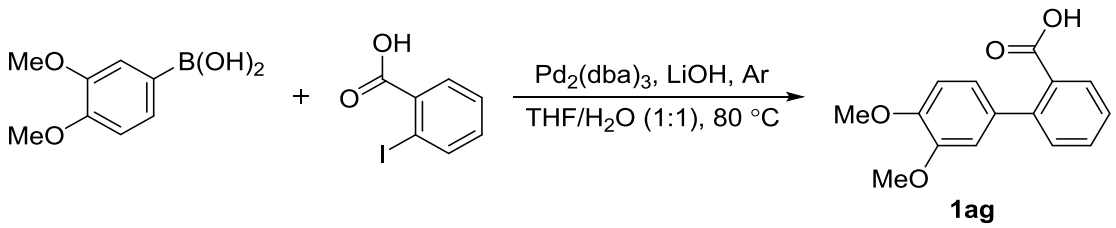
Following a modification of the reported procedure,[237] to a cooled solution of 3-methylindole (0.300 g, 2.29 mmol, 1.0 equiv) in DMF (5 mL) at 0 °C under Ar atmosphere was added sodium hydride (60% dispersion in mineral oil) (0.320 g, 8.00 mmol, 3.5 equiv). After stirring for 10 min at 0 °C, 3-chloro-2,2- dimethylpropionic acid (0.344 g, 2.51 mmol, 1.1 equiv) and potassium iodide (0.0380 g, 0.228 mmol, 0.10 equiv) were added and the reaction mixture was continued to stir at 0 °C for 15 min. The reaction mixture was then heated to 50 °C and continued to stir at 50 °C for 24 h. The reaction was quenched with water and acidified with 1 M HCl to pH 1. The aqueous layer was extracted with EtOAc (10 mL × 3) and the combined organic layers were washed with (10 mL × 1), brine once, dried over Na_2SO_4, and concentrated. Purification on a Combiflash purification system using a silica flash column (90:10 hexanes/EtOAc) afforded **1ae** (0.0850 g, 16%) as a colorless solid. Mp 72–74 °C; TLC (10% EtOAc/hexanes) R_f = 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.33 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.19 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.09 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.88 (d, *J* = 1.1 Hz, 1H), 4.27 (s, 2H), 2.31 (d, *J* = 1.1 Hz, 3H), 1.29 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.8, 137.7, 128.7, 126.6, 121.7, 119.1, 118.9, 111.2, 109.7, 53.6, 45.3, 23.8 (2C), 9.7; IR (neat) 3300–2100, 1700 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{18}NO_2$ $[M + H]^+$: 232.1338, found: 232.1315.



1af

2-(3-Methyl-1*H*-indol-1-yl)benzoic acid (1af):

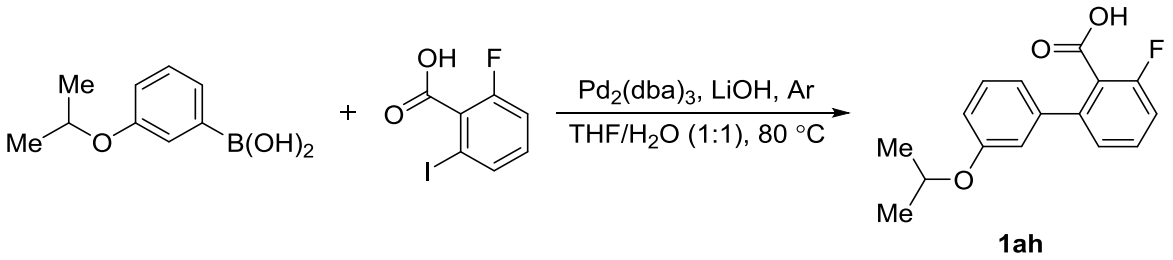
Following a slight modification of the reported procedure,[231] to a solution of 3-methyl-1*H*-indole (197 mg, 1.50 mmol, 1.0 equiv) and 2-iodobenzoic acid (372 mg, 1.50 mmol, 1.0 equiv) in anhydrous DMF (2.5 mL) in a flame-dried N_2-flushed microwave vial at rt was added potassium carbonate (207 mg, 1.50 mmol, 1.0 equiv) and copper(I) iodide (57.1 mg, 0.300 mmol, 0.20 equiv). The vial was sealed with a N_2 balloon inserted into a septum and the resulting suspension was stirred at 155 °C for 18 h (effervescence was observed and hood lights were kept off). Reaction mixture was quenched with 1.0 M aqueous HCl (10 mL), diluted with water (20 mL), and extracted with DCM (25 mL × 3). The combined organic layers were washed with water (60 mL × 3), brine (60 mL × 1), dried over Na_2SO_4, and concentrated. The oily residue obtained was dissolved in DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–2.5% MeOH/DCM over 50 min) afforded impure **1af** as an orange-brown oil. Repurification on a Combiflash purification system using a 12 g silica flash column (0–40% EtOAc/hexanes over 40 min) afforded a partial separation of pure **1af** (112 mg, 30%) as a creamish-orange solid. Mp 102–108 °C; TLC (5% MeOH/DCM) R_f = 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.66 (brs, 1H), 8.05–8.08 (m, 1H), 7.64–7.68 (m, 2H), 7.45–7.49 (m, 2H), 7.16–7.23 (m, 3H), 7.00 (d, *J* = 1.1 Hz, 1H), 2.42 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 139.7, 137.5, 133.8, 132.2, 129.6, 128.8, 127.3 (2C), 126.7, 122.5, 119.8, 119.3, 113.0, 109.9, 9.8; IR (neat) 3500–2200, 1690, 1600 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}NO_2$ $[M + H]^+$: 252.1025, found: 252.1013.



3',4'-Dimethoxy-[1,1'-biphenyl]-2-carboxylic acid (1ag):[238]

Following a modification of the reported procedure,[239] to a solution of (3,4-dimethoxyphenyl)boronic acid (287 mg, 1.58 mmol, 1.05 equiv) and 2-iodobenzoic acid (372 mg, 1.50 mmol, 1.0 equiv) in degassed THF (2.0 mL) in a flame-dried microwave vial at rt under Ar was added a sonicated solution of lithium hydroxide (90.0 mg, 3.75 mmol, 2.5 equiv) in degassed deionized water (2.0 mL) (solvents were degassed with Ar under sonication for 5 min) and the resulting slightly turbid solution was stirred at rt for 5 min (until effervescence ceased). The solution was degassed with Ar for 2 min followed by the addition of tris(dibenzylideneacetone)dipalladium (0) (20.6 mg, 0.0220 mmol, 0.015 equiv). The vial was sealed with a septum and the resulting suspension was stirred at 80 °C for 14 h. Reaction mixture was partially concentrated under N_2 and acidified with 2 M aqueous HCl solution (10 mL) followed by the addition of water (25 mL). The resulting suspension was extracted with DCM (25 mL × 3). The combined organic layers were washed with brine (50 mL × 1), dried over Na_2SO_4, and concentrated. The solid residue obtained was suspended in DCM containing few drops of MeOH and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–2% MeOH/DCM over 40 min) afforded **1ag** (235 mg, 61%) as a colorless solid with light orange tinge. Mp 164–166 °C (lit.[238] mp: 162–165 °C); TLC (4% MeOH/DCM, run twice) R_f = 0.52; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.77 (brs, 1H), 7.65 (dd, J = 8.0, 1.3 Hz, 1H), 7.53 (td, J = 7.6, 1.4 Hz, 1H), 7.42–7.39 (m, 2H), 6.99 (d, J = 8.3 Hz,

1H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.86 (dd, *J* = 8.2, 2.1 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.2, 148.3, 148.2, 140.4, 133.2, 132.7, 130.6, 130.3, 128.7, 126.8, 120.5, 112.2, 111.6, 55.5, 55.4; IR (neat) 3315, 1719 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{15}O_4$ $[M + H]^+$: 259.0970, found: 259.0957.

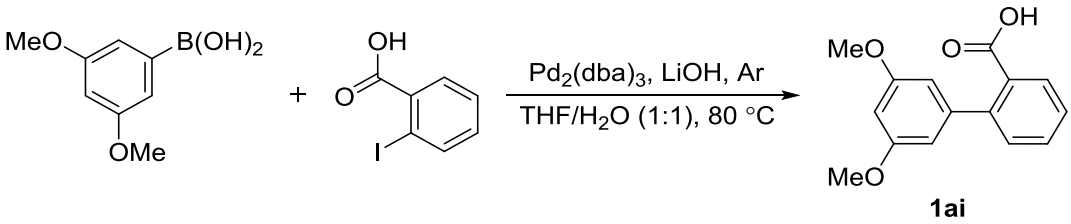


1ah

3-Fluoro-3'-isopropoxy-[1,1'-biphenyl]-2-carboxylic acid (1ah):

Following a modification of the reported procedure,[239] to a solution of (3-isopropoxyphenyl)boronic acid (283 mg, 1.58 mmol, 1.05 equiv) and 2-fluoro-6-iodobenzoic acid (399 mg, 1.50 mmol, 1.0 equiv) in degassed THF (2.0 mL) in a flame-dried microwave vial at rt under Ar was added a sonicated solution of lithium hydroxide (90.0 mg, 3.75 mmol, 2.5 equiv) in degassed deionized water (2.0 mL) (solvents were degassed with Ar under sonication for 5 min) and the resulting solution was stirred at rt for 5 min (until effervescence ceased). The solution was degassed with Ar for 1 min followed by the addition of tris(dibenzylideneacetone)dipalladium (0) (20.6 mg, 0.0220 mmol, 0.015 equiv). The vial was sealed with a septum and the resulting suspension was stirred at 80 °C for 13 h. Reaction mixture was partially concentrated under N_2 and acidified with 2 M aqueous HCl solution (15 mL) followed by the addition of water (20 mL). The resulting suspension was extracted with DCM (25 mL × 3). The combined organic layers were washed with brine (50 mL × 1), dried over Na_2SO_4, and concentrated. The oily residue obtained was redissolved in DCM and loaded on a silica gel in a sample cartridge. Purification on a

Combiflash purification system using a 24 g silica flash column (0–3% MeOH/DCM over 60 min) afforded impure **1ah** as a pale orange oil. Impure **1ah** was dissolved in 1.5 mL DMSO and loaded on a 50 g HP C18 Gold column. Repurification was carried out on a reverse-phase Combiflash system (0% ACN/H_2O both containing 0.1% CF3CO2H over 2 min followed by 0–70% ACN/H_2O both containing 0.1% CF_3CO_2H from 2–32 min). Elutions containing product were concentrated under vacuum in Genevac. The resulting colorless solid was dissolved in DCM and filtered through a short bed containing a mixture of Na_2SO_4 and silica gel using a phase separator. Concentration and drying under vacuum afforded pure **1ah** (262 mg, 64%) as a colorless partially oily crystalline solid. Mp 103–105 °C; TLC (3% MeOH/DCM) R_f = 0.19; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.91 (brs, 1H), 7.47 (m, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.14 (m, 1H), 6.99–6.92 (m, 3H), 4.57 (m, 1H), 1.35 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 160.0 (d, *J* = 252.5 Hz, 1C), 158.1, 143.0 (d, *J* = 2.3 Hz, 1C), 140.5 (d, *J* = 2.2 Hz, 1C), 131.9 (d, *J* = 9.1 Hz, 1C), 129.8, 125.9 (d, *J* = 3.1 Hz, 1C), 120.7, 120.5 (d, *J* = 15.8 Hz, 1C), 116.3, 115.8, 114.9 (d, *J* = 21.6 Hz, 1C), 70.4, 22.2 (2C); IR (neat) 3400–2400, 1738, 1704, 1573 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}FO_2$ $[M - OH]^+$: 257.0972, found: 257.0952.

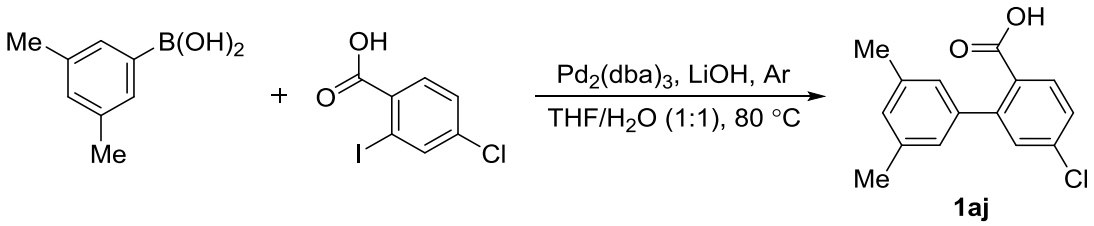


1ai

3',5'-Dimethoxy-[1,1'-biphenyl]-2-carboxylic acid (1ai):[240]

Following a modification of the reported procedure,[239] to a suspension of (3,5-dimethoxyphenyl)boronic acid (287 mg, 1.58 mmol, 1.05 equiv) and 2-iodobenzoic acid (372 mg, 1.50 mmol, 1.0 equiv) in degassed THF (2.0 mL) in a flame-dried microwave vial at rt under Ar

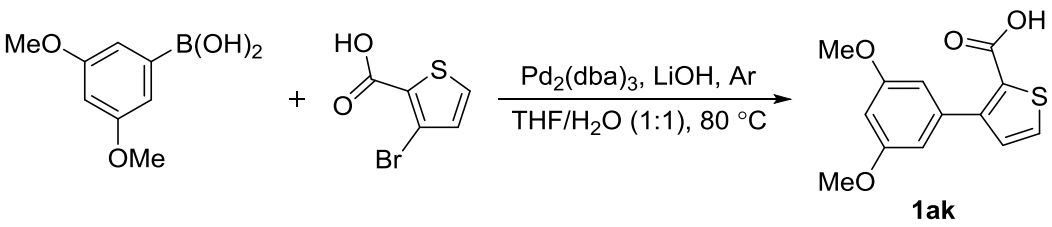
was added a a sonicated solution of lithium hydroxide (90.0 mg, 3.75 mmol, 2.5 equiv) in degassed deionized water (2.0 mL) (solvents were degassed with Ar under sonication for 5 min) and the resulting slightly turbid solution was stirred at rt for 5 min (until effervescence ceased). The solution was degassed with Ar for 2 min followed by the addition of tris(dibenzylideneacetone)dipalladium (0) (20.6 mg, 0.0220 mmol, 0.015 equiv). The vial was sealed with a septum and the resulting suspension was stirred at 80 °C for 14 h. Reaction mixture was partially concentrated under N_2 and acidified with 2 M aqueous HCl solution (10 mL) followed by the addition of water (15 mL). The resulting suspension was extracted with DCM (25 mL × 3). The combined organic layers were washed with brine (50 mL × 1), dried over Na_2SO_4, and concentrated. The residue obtained was redissolved in DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 24 g silica flash column (0–1% MeOH/DCM over 40 min) afforded impure **1ai** as a cream solid. Recrystallization of the solid from DCM/ether mixture (suspended solid in ether was dissolved by the dropwise addition of DCM. Hexanes was then added until the solution became slightly turbid) afforded pure **1ai** (232 mg, 60%) as a colorless small plate-like crystals after filtration and drying under vacuum. Mp 145.5–147 °C; TLC (3% MeOH/DCM) R_f = 0.32; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.81 (brs, 1H), 7.93 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.55 (td, *J* = 7.5, 1.4 Hz, 1H), 7.45–7.38 (m, 2H), 6.51 (d, *J* = 2.2 Hz, 2H), 6.47 (t, *J* = 2.2 Hz, 1H), 3.80 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 160.6 (2C), 143.23, 143.18, 132.1, 131.1, 130.6, 129.7, 127.5, 107.0 (2C), 99.9, 55.6 (2C); IR (neat) 3300–2300, 1682, 1592 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{15}O_4$ $[M + H]^+$: 259.0970, found: 259.0960.



5-Chloro-3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid (1aj):

Following a modification of the reported procedure,[239] to a solution of (3,5-dimethylphenyl)boronic acid (236 mg, 1.58 mmol, 1.05 equiv) and 4-chloro-2-iodobenzoic acid (424 mg, 1.50 mmol, 1.0 equiv) in degassed THF (2.0 mL) in a flame-dried microwave vial at rt under Ar was added a a sonicated solution of lithium hydroxide (90.0 mg, 3.75 mmol, 2.5 equiv) in degassed deionized water (2.0 mL) (solvents were degassed with Ar under sonication for 5 min) and the resulting solution was stirred at rt for 5 min (until effervescence ceased). The solution was degassed with Ar for 2 min followed by the addition of tris(dibenzylideneacetone)dipalladium (0) (20.6 mg, 0.0220 mmol, 0.015 equiv). The vial was sealed with a septum and the resulting suspension was stirred at 80 °C for 14 h. Reaction mixture was partially concentrated under N_2 and acidified with 2 M aqueous HCl solution (10 mL) followed by the addition of water (25 mL). The resulting suspension was extracted with DCM (25 mL × 3). The combined organic layers were washed with brine (50 mL × 1), dried over Na_2SO_4, and concentrated. The solid residue obtained was suspended in DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–40% EtOAc/hexanes over 40 min) afforded impure **1aj** as a creamish-orange solid. Impure **1aj** was dissolved in 1.5 mL DMSO and loaded on a 50 g HP C18 Gold column. Repurification was carried out on a reverse-phase Combiflash system (0% ACN/H_2O both containing 0.1% CF_3CO_2H over 2 min followed by 0–70% ACN/H_2O both containing 0.1% CF_3CO_2H from 2–32 min). Elutions containing product were

concentrated under vacuum in Genevac. The resulting creamish solid was dissolved in ether and filtered through a short bed containing a mixture of Na_2SO_4 and silica gel using a phase separator tabless. Concentration and drying under vacuum afforded pure **1aj** (320 mg, 82%) as a pale creamish-orange crystalline solid. Mp 154–156 °C; TLC (30% EtOAc/hexanes) R_f = 0.22; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (brs, 1H), 7.88 (m, 1H), 7.39–7.36 (m, 2H), 7.01 (s, 1H), 6.93 (s, 2H), 2.34 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 145.7, 139.8, 138.4, 137.8 (2C), 132.3, 131.5, 129.7, 127.7, 127.3, 126.3 (2C), 21.5 (2C); IR (neat) 3350–2150, 1687 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{12}ClO$ $[M - OH]^+$: 243.0571, found: 243.0566.

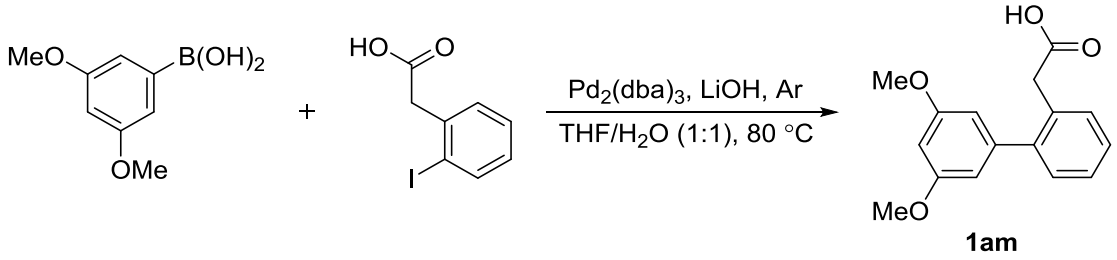


1ak

3-(3,5-Dimethoxyphenyl)thiophene-2-carboxylic acid (1ak):

Following a modification of the reported procedure,[239] to a suspension of (3,5-dimethoxyphenyl)boronic acid (287 mg, 1.58 mmol, 1.05 equiv) and 3-bromothiophene-2-carboxylic acid (311 mg, 1.50 mmol, 1.0 equiv) in degassed THF (2.0 mL) in a flame-dried microwave vial at rt under Ar was added a sonicated solution of lithium hydroxide (90.0 mg, 3.75 mmol, 2.5 equiv) in degassed deionized water (2.0 mL) (solvents were degassed with Ar under sonication for 5 min) and the resulting slightly turbid solution was stirred at rt for 5 min (until effervescence ceased). The solution was degassed with Ar for 2 min followed by the addition of tris(dibenzylideneacetone)dipalladium (0) (20.6 mg, 0.0220 mmol, 0.015 equiv). The vial was sealed with a septum and the resulting suspension was stirred at 80 °C for 14 h. Reaction mixture was partially concentrated under N_2 and acidified with 2 M aqueous HCl solution (10 mL) followed

by the addition of water (15 mL). The resulting suspension was extracted with DCM (25 mL × 3). The combined organic layers were washed with brine (50 mL × 1), dried over Na_2SO_4, and concentrated. The solid residue obtained was suspended in DCM containing few drops of MeOH and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–2% MeOH/DCM over 40 min) afforded impure **1ak** as a cream-orange solid. Impure **1ak** was dissolved in 2.0 mL DMSO and loaded on a 50 g HP C18 Gold column. Repurification on a Combiflash system (0% ACN/H_2O both containing 0.1% CF_3CO_2H over 2 min followed by 0–70% ACN/H_2O both containing 0.1% CF_3CO_2H from 2–32 min). Elutions containing product were concentrated under vacuum in Genevac. The resulting colorless solid was dissolved in DCM and filtered through a short bed containing a mixture of Na_2SO_4 and silica gel using a phase separator tabless. Concentration and drying under vacuum afforded pure **1ak** (120 mg, 30%) as a colorless solid. Mp 147.5–149 °C; TLC (3% MeOH/DCM) R_f = 0.29; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.18 (brs, 1H), 7.57 (d, *J* = 5.1 Hz, 1H), 7.10 (d, *J* = 5.1 Hz, 1H), 6.61 (d, *J* = 2.3 Hz, 2H), 6.50 (t, *J* = 2.3 Hz, 1H), 3.81 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 160.4 (2C), 149.8, 137.4, 132.1, 131.9, 126.9, 107.7 (2C), 100.6, 55.6 (2C); IR (neat) 3300–2300, 1686, 1597 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}O_4S$ $[M + H]^+$: 265.0535, found: 265.0524.



1am

2-(3',5'-dimethoxy-[1,1'-biphenyl]-2-yl)acetic acid (1am):

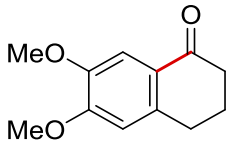
Following a modification of the reported procedure,[239] to a solution of (3,5-dimethoxyphenyl)boronic acid (147 mg, 0.807 mmol, 1.05 equiv) and 2-iodophenylacetic acid (200 mg, 0.763 mmol, 1.0 equiv) in degassed THF (2.0 mL) in a flame-dried microwave vial at rt under Ar was added a sonicated solution of lithium hydroxide (46.0 mg, 1.91 mmol, 2.5 equiv) in degassed deionized water (2.0 mL) (solvents were degassed with Ar under sonication for 5 min) and the resulting slightly turbid solution was stirred at rt for 5 min (until effervescence ceased). The solution was degassed with Ar for 2 min followed by the addition of tris(dibenzylideneacetone)dipalladium (0) (10.5 mg, 0.0114 mmol, 0.015 equiv). The vial was sealed with a septum and the resulting suspension was stirred at 80 °C for 14 h. The reaction mixture was partially concentrated under N_2 and acidified with 2 M aqueous HCl solution (10 mL) followed by the addition of water (25 mL). The resulting suspension was extracted with DCM (25 mL × 3). The combined organic layers were washed with brine (50 mL × 1), dried over Na_2SO_4, and concentrated. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **1am** (150 mg, 72%) as a colorless solid. Mp 128–130 °C; TLC (50% EtOAc/hexanes) R_f = 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.27 (m, 4H), 6.47 (s, 3H), 3.78 (s, 6H), 3.65 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 160.7 (2C), 143.0, 142.7, 131.1, 130.5, 130.1, 127.8, 127.5, 107.5 (2C), 99.8, 55.5 (2C), 38.5; IR (neat) 3400–2200, 1687, 1592 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{17}O_4$ $[M + H]^+$: 273.1127, found: 273.1098.

General procedure C for the Friedel–Crafts reaction in HFIP (Figure 11): Procedure (Step 1 → Synthesis of Acid Chloride):

To a solution of acid **1** (0.300 mmol, 1.0 equiv) in anhydrous DCM (1.5 mL) in a flame-dried N_2-flushed 2-dram vial at rt under N_2 blanket was added a small drop (using a 21G needle) of DMF. Then oxalyl chloride (0.390 or 0.600 mmol, 1.3 or 2.0 equiv) was added dropwise (gas evolution was observed; the cap was opened for a while under N_2 blanket to release the pressure) and the reaction mixture was stirred at rt for a specified period (25–90 min). The reaction mixture was concentrated under N_2 using sample concentrator and the residue obtained was dried under vacuum for ca.15–20 min. The crude acid chloride **2** was used as such for the Step 2.

Procedure (Step 2 → Friedel–Crafts Acylation):

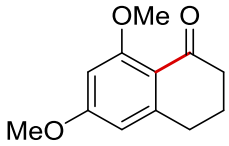
To the same 2-dram vial containing the crude acid chloride intermediate **2** at rt was added HFIP (0.75 mL, substrate concentration is 0.40 M) quickly and the vial was capped immediately. The resultant reaction mixture was stirred at rt for 2–6 h. The reaction mixture was concentrated under N_2 and the resulting residue was dissolved in a minimum quantity of DCM or ether and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a normal phase silica flash column (4, 12, or 24 g) afforded the cyclized product **3** after concentration and drying under vacuum.



3a

6,7-Dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one (3a):[178,179]

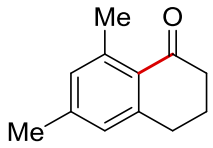
Following the general procedure **C**, 4-(3,4-dimethoxyphenyl)butanoic acid **1a** (67.3 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(3,4-dimethoxyphenyl)butanoyl chloride **2a** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2a** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 2 h. Purification on a Combiflash purification system using a 4 g silica flash column (0–40% EtOAc/hexanes over 20 min) afforded **3a** (59.9 mg, 97%) as a colorless solid. The spectral data matched literature values.



3b

6,8-Dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one (3b):[180]

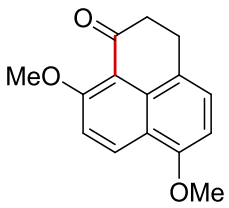
Following the general procedure **C**, 4-(3,5-dimethoxyphenyl)butanoic acid **1b** (67.3 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(3,5-dimethoxyphenyl)butanoyl chloride **2b** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2b** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **3b** (53.0 mg, 86%) as a brown solid. Mp 64–66 °C; TLC (50% EtOAc/hexanes) R_f = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36–6.28 (m, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 2.92–2.83 (m, 2H), 2.63–2.52 (m, 2H), 2.06–1.96 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.2, 164.0, 162.8, 149.4, 116.6, 104.8, 97.4, 56.1, 55.5, 40.9, 31.8, 23.0; IR (neat) 1665, 1596 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}O_3$ $[M + H]^+$: 207.1021, found: 207.0998.



3c

6,8-Dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (3c):[241]

Following the general procedure **C**, 4-(3,5-dimethylphenyl)butanoic acid **1c** (57.6 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(3,5-dimethylphenyl)butanoyl chloride **2c** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2c** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (80:20 hexanes/EtOAc) afforded **3c** (38.0 mg, 73%) as a yellow oil. The spectral data matched literature values.



3d

6,9-Dimethoxy-2,3-dihydro-1*H*-phenalen-1-one (3d):

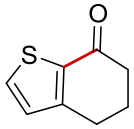
Following the general procedure **C**, 3-(4,7-dimethoxynaphthalen-1-yl)propanoic acid **1d** (78.1 mg, 0.300 mmol, 1.0 equiv) was converted to 3-(4,7-dimethoxynaphthalen-1-yl)propanoyl chloride **2d** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2d** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 4 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–50% EtOAc/hexanes over 50 min) afforded **3d** (37.0 mg, 51%) as an olive green solid. Mp 124–127 °C; TLC (30% EtOAc/hexanes) R_f = 0.22; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 9.4 Hz, 1H), 7.27–7.24 (m,

2H), 6.64 (d, J = 7.8 Hz, 1H), 4.03 (s, 3H), 3.96 (s, 3H), 3.24 (apparent t, J = 7.2 Hz, 2H), 2.85 (apparent t, J = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1, 158.3, 154.6, 134.6, 130.2, 126.4, 124.5, 120.1, 115.8, 112.6, 102.1, 56.7, 55.7, 40.8, 28.8; IR (neat) 1676, 1588, 1248, 1042 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{15}O_3$ $[M + H]^+$: 243.1021, found: 243.1006.

3e

6,7-Dihydrobenzo[*b*]thiophen-4(5*H*)-one (3e):[183]

Following the general procedure **C**, 4-(2-thienyl)butyric acid **1e** (51.1 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(2-thienyl)butanoyl chloride **2e** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2e** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 3 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–15% EtOAc/hexanes over 30 min) afforded **3e** (37.0 mg, 81%) as a pale yellow oil. The spectral data matched literature values.

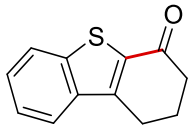


3f

5,6-Dihydrobenzo[*b*]thiophen-7(4*H*)-one (3f):[185]

Following the general procedure **C**, 4-(thiophen-3-yl)butanoic acid **1f** (51.0 mg, 0.300 mmol, 1 equiv) was converted to 4-(thiophen-3-yl)butanoyl chloride **2f** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2f** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification

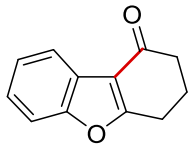
system using a silica flash column (80:20 hexanes/EtOAc) afforded **3f** (33.0 mg, 72%) as a colorless oil. TLC (20% EtOAc/hexanes) R_f = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 4.9 Hz, 1H), 6.97 (d, *J* = 4.9 Hz, 1H), 2.88 (t, *J* = 6.1 Hz, 2H), 2.69–2.50 (m, 2H), 2.18 (tt, *J* = 6.5, 5.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4, 152.7, 136.7, 133.9, 128.3, 38.4, 26.2, 24.5; IR (neat) 1653 cm^{-1}; HRMS (ESI) *m/z* calcd for C_8H_9OS $[M + H]^+$: 153.0374, found: 153.0350.



3g

2,3-Dihydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (3g):[225]

Following the general procedure **C**, 4-(benzo[*b*]thiophen-3-yl)butanoic acid **1g** (66.0 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(benzo[*b*]thiophen-3-yl)butanoyl chloride **2g** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2g** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **3g** (60.0 mg, 99%) as a colorless solid. The spectral data matched literature values.

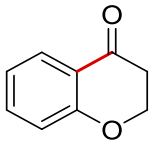


3h

3,4-Dihydrodibenzo[*b*,*d*]furan-1(2*H*)-one (3h):[242]

Following the general procedure **C**, 4-(benzofuran-2-yl)butanoic acid **1h** (61.0 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(benzofuran-2-yl)butanoyl chloride **2h** using oxalyl chloride (50.8

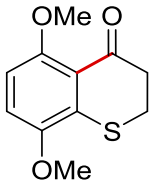
μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2h** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (80:20 hexanes/EtOAc) afforded **3h** (50.0 mg, 90%) as a colorless oil. The spectral data matched literature values.



3i

Chroman-4-one (3i):[243]

Following the general procedure **C**, 3-phenoxypropanoic acid **1i** (49.8 mg, 0.300 mmol, 1.0 equiv) was converted to 3-phenoxypropanoyl chloride **2i** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2i** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (80:20 hexanes/EtOAc) afforded **3i** (31.0 mg, 70%) as a colorless oil. The spectral data matched literature values.

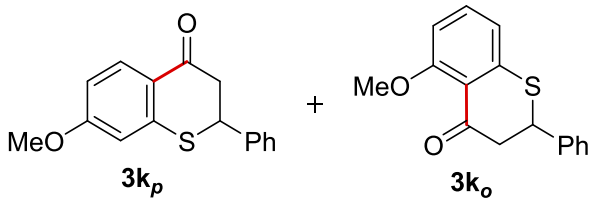


3j

5,8-Dimethoxythiochroman-4-one (3j):[191]

Following the general procedure **C**, 3-((2,5-dimethoxyphenyl)thio)propanoic acid **1j** (72.7 mg, 0.300 mmol, 1.0 equiv) was converted to 3-((2,5-dimethoxyphenyl)thio)propanoyl chloride **2j** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2j** was

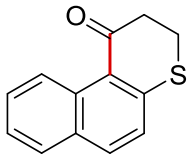
dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–50% EtOAc/hexanes over 50 min) afforded **3j** (35.5 mg, 53%) as a creamish yellow solid. Mp 133–136 °C; TLC (40% EtOAc/hexanes) R_f = 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, *J* = 9.0 Hz, 1H), 6.64 (d, *J* = 9.0 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.16–3.13 (m, 2H), 2.93–2.90 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 155.4, 149.0, 133.7, 122.2, S39 115.1, 108.4, 56.8, 56.7, 41.0, 25.5; IR (neat) 1677, 1575 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{11}H_{13}O_3S$ $[M + H]^+$: 225.0585, found: 225.0578.



7-Methoxy-2-phenylthiochroman-4-one (3k$_p$) and 5-Methoxy-2-phenylthiochroman-4-one (3k$_o$):

Following the general procedure **C**, 3-((3-methoxyphenyl)thio)-3-phenylpropanoic acid **1k** (86.5 mg, 0.300 mmol, 1.0 equiv) was converted to 3-((3-methoxyphenyl)thio)-3-phenylpropanoyl chloride **2k** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2k** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 4 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–20% EtOAc/hexanes over 40 min) afforded **3k$_p$** (50.0 mg, 62%) and **3k$_o$** (10.8 mg, 13%) as light yellow solids (combined yield = 60.8 mg, 75%; **3k$_p$**:**3k$_o$** = 82:18). For **3k$_p$**: Mp 82.5–84.5 °C; TLC (20% EtOAc/hexanes) R_f = 0.52; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.13 (m, 1H), 7.31–7.43 (m, 5H), 6.73–6.75 (m, 2H), 4.71 (dd, *J* = 12.9, 3.1 Hz, 1H), 3.83 (s, 3H), 3.27 (dd, *J* = 16.5, 12.9 Hz, 1H),

3.15 (dd, *J* = 16.5, 3.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.2, 163.7, 144.4, 138.7, 131.5, 129.1, 128.6, 127.6, 124.3, 112.9, 110.6, 55.7, 46.6, 45.9; IR (neat) 1665, 1587 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{15}O_2S$ $[M + H]^+$: 271.0793, found: 271.0787. For **3k$_o$**: Mp 110.5–113.5 °C; TLC (20% EtOAc/hexanes) R_f = 0.22; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.43 (m, 6H), 6.87 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.74 (m, 1H), 4.69 (dd, *J* = 13.0, 3.2 Hz, 1H), 3.91 (s, 3H), 3.34 (dd, *J* = 15.7, 13.0 Hz, 1H), 3.18 (dd, *J* = 15.7, 3.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.4, 161.6, 144.3, 138.7, 133.9, 129.2, 128.6, 127.6, 121.0, 119.5, 109.0, 56.4, 48.9, 45.4; IR (neat) 1672, 1579 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{15}O_2S$ $[M + H]^+$: 271.0793, found: 271.0789.

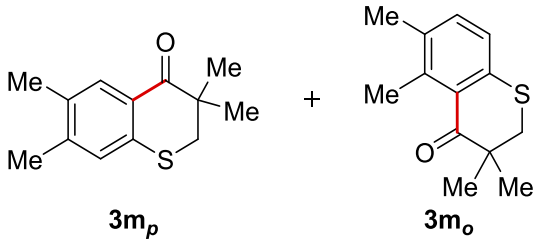


3l

2,3-Dihydro-1*H*-benzo[*f*]thiochromen-1-one (3l):[192]

Following the general procedure **C**, 3-(2-naphthylthio)propionic acid **1l** (69.7 mg, 0.300 mmol, 1.0 equiv) was converted to 3-(2-naphthylthio)propionyl chloride **2l** using oxalyl chloride (50.8 µL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2l** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 3 h. Purification on a Combiflash purification system using a 4 g silica flash column (0–5% EtOAc/hexanes over 50 min) afforded **3l** (59.4 mg, 92%) as a pale yellow turbid oil. TLC (10% ether/hexanes, run twice) R_f = 0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (m, 1H), 7.73 (m, 2H), 7.60 (ddd, *J* = 8.6, 6.9, 1.5 Hz, 1H), 7.44 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 3.27 (m, 2H), 3.09 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.2, 145.3, 133.7, 132.6, 131.9, 129.3, 128.6, 126.3, 125.79, 125.77, 125.5,

41.4, 26.5; IR (neat) 1657, 1588 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{11}OS$ $[M + H]^+$: 215.0531, found: 215.0528.

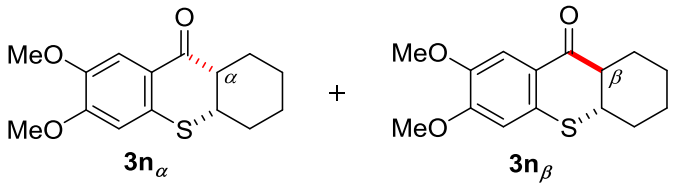


$3m_p$ $3m_o$

3,3,6,7-Tetramethylthiochroman-4-one ($3m_p$) and 3,3,5,6-Tetramethylthiochroman-4-one ($3m_o$):

Following the general procedure **C**, 3-((3,4-dimethylphenyl)thio)-2,2-dimethylpropanoic acid **1m** (71.5 mg, 0.300 mmol, 1.0 equiv) was converted to 3-((3,4-dimethylphenyl)thio)-2,2-dimethylpropanoyl chloride **2m** using oxalyl chloride (50.8 µL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2m** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 3 h. Purification on a Combiflash purification system using a 24 g silica flash column (0–10% EtOAc/hexanes over 20 min) afforded a partial separation of $\mathbf{3m_p}$ (39.5 mg) as a colorless solid and $\mathbf{3m_o}$ (19.0 mg) as a colorless oily solid and a small amount (5.00 mg) was obtained as a mixture of $\mathbf{3m_p}$ and $\mathbf{3m_o}$ (combined yield = 63.5 mg, 96%; $\mathbf{3m_p}$:$\mathbf{3m_o}$ = 64:36). For $\mathbf{3m_p}$: Mp 89–90.5 °C; TLC (4% EtOAc/hexanes) R_f = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 6.98 (s, 1H), 3.04 (s, 2H), 2.23 (d, *J* = 3.5 Hz, 6H), 1.30 (s, 6H); ^{13}C NMR (101 MHz, CDCl3) δ 198.6, 143.1, 138.5, 133.9, 130.9, 128.0, 127.7, 41.1, 39.6, 23.8 (2C), 20.0, 19.3; IR (neat) 1671, 1597 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}OS$ $[M + H]^+$: 221.1000, found: 221.0970. For $\mathbf{3m_o}$: TLC (4% EtOAc/hexanes) R_f = 0.43; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 3.00 (s, 2H), 2.35 (s, 3H), 2.25 (s, 3H), 1.32 (s, 6H); ^{13}C NMR (101 MHz,

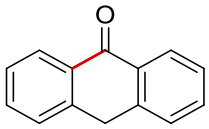
$CDCl_3$) δ 203.3, 140.4, 138.7, 135.4, 133.2, 132.1, 124.8, 44.7, 40.5, 24.3 (2C), 20.6, 18.0; IR (neat) 1676 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}OS$ $[M + H]^+$: 221.1000, found: 221.0992.



Rel-(4a*S*,9a*S*)-6,7-Dimethoxy-2,3,4,4a-tetrahydro-1*H*-thioxanthen-9(9a*H*)-one ($3n_\alpha$) and Rel- (4a*S*,9a*R*)-6,7-Dimethoxy-2,3,4,4a-tetrahydro-1*H*-thioxanthen-9(9a*H*)-one ($3n_\beta$):

Following the general procedure **C**, rel-(1*S*,2*S*)-2-((3,4-dimethoxyphenyl)thio)cyclohexanecarboxylic acid] **1n** (88.9 mg, 0.300 mmol, 1.0 equiv) was converted to rel-(1*S*,2*S*)-2-((3,4-dimethoxyphenyl)thio)cyclohexanecarbonyl chloride] **2n** with oxalyl chloride (50.8 µL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2n** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 3 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–20% EtOAc/hexanes over 40 min) afforded a partial separation of $\mathbf{3n}_\alpha$ (17.5 mg) and remaining as a mixture of $\mathbf{3n}_\alpha$ and $\mathbf{3n}_\beta$ (65.4 mg) as very pale orange viscous oils (combined yield = 82.9 mg, 99%; $\mathbf{3n}_\alpha$:$\mathbf{3n}_\beta$ = 93:7). For $\mathbf{3n}_\alpha$: TLC (20% EtOAc/hexanes, run twice) R_f = 0.59; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 1H), 6.63 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.73 (brs, 1H), 2.82 (m, 1H), 2.24 (m, 1H), 1.90–1.74 (complex, 3H), 1.65 (m, 1H), 1.57–1.48 (complex, 2H), 1.47–1.40 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.9, 153.9, 147.2, 135.2, 123.0, 110.8, 109.0, 56.4, 56.2, 48.9, 43.2, 29.9, 24.9, 23.9, 23.2; IR (neat) 1656, 1592 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{19}O_3S$ $[M + H]^+$: 279.1055, found: 279.1046. For $\mathbf{3n}_\beta$: TLC (20% EtOAc/hexanes, run twice) R_f = 0.64; Characteristic peaks only for $\mathbf{3n}_\beta$ in a mixture ($\mathbf{3n}_\alpha$:$\mathbf{3n}_\beta$ = ca. 91:9): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 6.59 (s, 1H),

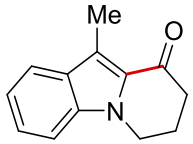
3.87 (s, 3H), 3.86 (s, 3H), 3.31 (td, *J* = 12.2, 4.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.0, 153.6, 135.3, 123.8, 110.9, 108.6, 51.7, 45.3, 32.2, 26.4, 25.5, 25.4.



3o

Anthracen-9(10*H*)-one (3o):[244]

Following the general procedure **C**, *α*-phenyl-*o*-toluic acid **1o** (63.6 mg, 0.300 mmol, 1.0 equiv) was converted to 2-benzylbenzoyl chloride **2o** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2o** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (90:10 hexanes/EtOAc) afforded **3o** (45.0 mg, 77%) as a colorless solid. The spectral data matched literature values.

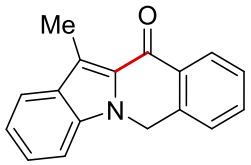


3p

10-Methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (3p):[245]

Following the general procedure **C**, 4-(3-methyl-1*H*-indol-1-yl)butanoic acid **1p** (65.0 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(3-methyl-1*H*-indol-1-yl)butanoyl chloride **2p** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2p** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a

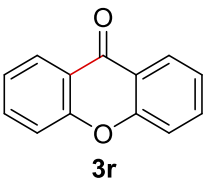
Combiflash purification system using a silica flash column (80:20 hexanes/EtOAc) afforded **3p** (43.0 mg, 72%) as a brown solid. The spectral data matched literature values.



3q

12-Methylindolo[1,2-*b*]isoquinolin-11(6*H*)-one (3q):

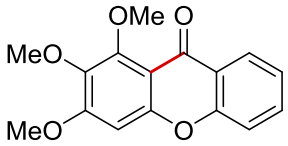
Following the general procedure **C**, 2-((3-methyl-1*H*-indol-1-yl)methyl)benzoic acid **1q** (79.6 mg, 0.300 mmol, 1.0 equiv) was converted to 2-((3-methyl-1*H*-indol-1-yl)methyl)benzoyl chloride **2q** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 90 min. The crude acid chloride **2q** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **3q** (54.0 mg, 73%) as a yellow solid. Mp 203–205 °C; TLC (50% EtOAc/hexanes) R_f = 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.79 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.63 (td, *J* = 7.5, 1.4 Hz, 1H), 7.56–7.50 (m, 1H), 7.49–7.41 (m, 3H), 7.25–7.20 (m, 1H), 5.46 (s, 2H), 2.90–2.77 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9, 136.8, 136.1 (2C), 133.0, 131.8, 128.2, 128.1, 127.3, 126.3, 126.2, 121.7, 120.8, 120.3, 110.1, 44.6, 10.5; IR (neat) 1644 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}NO$ $[M + H]^+$: 248.1075, found: 248.1053.



3r

9*H*-Xanthen-9-one (3r):[199]

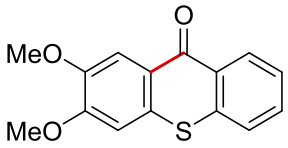
Following the general procedure **C**, 2-phenoxybenzoic acid **1r** (64.3 mg, 0.300 mmol, 1.0 equiv) was converted to 2-phenoxybenzoyl chloride **2r** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 45 min. The crude acid chloride **2r** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 4 h. Purification on a Combiflash purification system using a 4 g silica flash column (0– 5% EtOAc/hexanes over 50 min) afforded **3r** (45.4 mg, 77%) as a colorless solid. The spectral data matched literature values.



3s

1,2,3-Trimethoxy-9*H*-xanthen-9-one (3s):[200]

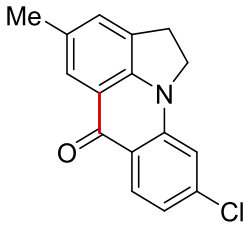
Following the general procedure **C**, 2-(3,4,5-trimethoxyphenoxy)benzoic acid **1s** (91.0 mg, 0.300 mmol, 1.0 equiv) was converted to 2-(3,4,5-trimethoxyphenoxy)benzoyl chloride **2s** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 60 min. The crude acid chloride **2s** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **3s** (80.0 mg, 93%) as a colorless solid. Mp 125–127 °C; TLC (50% EtOAc/hexanes) R_f = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.65 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.41–7.37 (m, 1H), 7.34 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 6.74 (s, 1H), 4.03 (s, 3H), 3.98 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 158.9, 155.3, 154.7, 153.7, 139.7, 134.0, 126.8, 124.0, 122.6, 117.2, 111.0, 96.2, 62.2, 61.7, 56.4; IR (neat) 2946, 1650, 1598 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{15}O_5$ $[M + H]^+$: 287.0919, found: 287.0916.



3t

2,3-Dimethoxy-9*H*-thioxanthen-9-one (3t):[201]

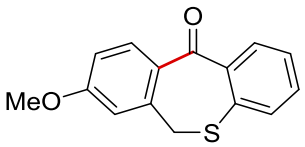
Following the general procedure **C**, 2-((3,4-dimethoxyphenyl)thio)benzoic acid **1t** (87.1 mg, 0.300 mmol, 1.0 equiv) was converted to 2-((3,4-dimethoxyphenyl)thio)benzoyl chloride **2t** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 60 min. The crude acid chloride **2t** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 2.5 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–40% EtOAc/hexanes over 40 min) afforded **3t** (76.3 mg, 93%) as a creamish-yellow solid. Mp 174.5–177.5 °C (lit.[201] mp: 172–173 °C); TLC (2% MeOH/DCM) R_f = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (m, 1H), 7.99 (s, 1H), 7.56–7.48 (m, 2H), 7.43 (m, 1H), 6.84 (s, 1H), 3.98 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 153.5, 148.8, 137.1, 131.7, 131.4, 129.8, 128.8, 126.2, 125.9, 123.3, 110.2, 106.7, 56.4, 56.3; IR (neat) 1625, 1588 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{13}O_3S$ $[M + H]^+$: 273.0585, found: 273.0552.



3u

9-Chloro-4-methyl-1*H*-pyrrolo[3,2,1-*de*]acridin-6(2*H*)-one (3u):

Following the general procedure **C**, 4-chloro-2-(5-methylindolin-1-yl)benzoic acid (ca. 94% pure) **1u** (86.3 mg, 0.300 mmol, 1.0 equiv) was converted to 4-chloro-2-(5-methylindolin-1-yl)benzoyl chloride **2u** using oxalyl chloride (33.0 μL, 0.390 mmol, 1.3 equiv) in 25 min (oxalyl chloride was added over 5 min). The crude acid chloride **2u** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 3 h. Purification on a Combiflash purification system using a 12 g silica flash column (0– 5% MeOH/DCM over 50 min) provided impure **3u** as an insoluble yellow fluorescent solid. Trituration of impure **3u** with CD_2Cl_2 and filtration under suction (including additional washings by CD_2Cl_2) afforded pure **3u** (66.2 mg, 82%) as a bright yellow fluorescent solid (almost insoluble in all solvents). TLC (2% MeOH/DCM) R_f = 0.27; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.41 (d, *J* = 8.7 Hz, 1H), 7.83 (m, 1H), 7.39 (m, 1H), 7.30 (d, *J* = 1.9 Hz, 1H), 7.21 (dd, *J* = 8.7, 1.9 Hz, 1H), 4.49 (dd, *J* = 8.4, 7.7 Hz, 2H), 3.57 (t, *J* = 8.0 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 176.7, 144.1, 140.8, 139.6, 133.1, 132.5, 130.2, 130.0, 122.3, 121.7, 121.5, 119.1, 114.1, 49.0, 28.1, 21.6; IR (neat) 1627, 1610 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{13}ClNO$ $[M + H]^+$: 270.0686, found: 270.0678.

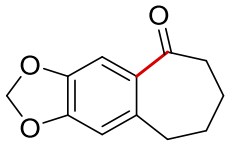


3v

8-Methoxydibenzo[*b*,*e*]thiepin-11(6*H*)-one (3v):[179,202]

Following the general procedure **C**, 2-((3-methoxybenzyl)thio)benzoic acid **1v** (82.3 mg, 0.300 mmol, 1.0 equiv) was converted to 2-((3-methoxybenzyl)thio)benzoyl chloride **2v** with oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 60 min. The crude acid chloride **2v** was dissolved in

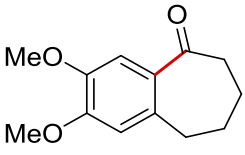
HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 4 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–10% EtOAc/hexanes over 50 min) afforded **3v** (62.3 mg, 81%) as a colorless solid. The spectral data matched literature values.



3w

6,7,8,9-Tetrahydro-5*H*-cyclohepta[4,5]benzo[1,2-*d*][1,3]dioxol-5-one (3w):

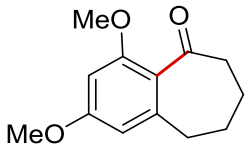
Following the general procedure **C**, 5-(benzo[*d*][1,3]dioxol-5-yl)pentanoic acid **1w** (66.7 mg, 0.300 mmol, 1.0 equiv) was converted to 5-(benzo[*d*][1,3]dioxol-5-yl)pentanoyl chloride **2w** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2w** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 6 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–20% EtOAc/hexanes over 40 min) afforded **3w** (36.3 mg, 59%) as a pale yellow viscous oil. TLC (30% EtOAc/hexanes) R_f = 0.66; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.63 (s, 1H), 5.97 (s, 2H), 2.84 (m, 2H), 2.68 (m, 2H), 1.86–1.73 (complex, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9, 151.1, 146.8, 138.4, 132.8, 109.8, 108.8, 101.8, 40.8, 32.7, 25.2, 20.6; IR (neat) 1660, 1615 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{13}O_3$ $[M + H]^+$: 205.0865, found: 205.0844.



3x

2,3-Dimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one (3x):[246]

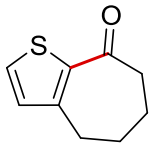
Following the general procedure **C**, 5-(3,4-dimethoxyphenyl)pentanoic acid **1x** (71.4 mg, 0.300 mmol, 1.0 equiv) was converted to 5-(3,4-dimethoxyphenyl)pentanoyl chloride **2x** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid **2x** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (80:20 hexanes/EtOAc) afforded **3x** (37.0 mg, 56%) as a colorless solid. The spectral data matched literature values.



3y

2,4-Dimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one (3y):

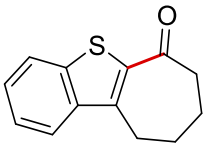
Following the general procedure **C**, 5-(3,5-dimethoxyphenyl)pentanoic acid **1y** (65.0 mg, 0.300 mmol, 1.0 equiv) was converted to 5-(3,5-dimethoxyphenyl)pentanoyl chloride **2y** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2y** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using S46 a silica flash column (50:50 hexanes/EtOAc) afforded **3y** (40.0 mg, 61%) as a colorless oil. TLC (50% EtOAc/hexanes) R_f = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (d, *J* = 2.2 Hz, 1H), 6.26 (d, *J* = 2.2 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 2.72 (dd, *J* = 7.1, 5.4 Hz, 2H), 2.67–2.54 (m, 2H), 1.77 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.7, 162.3, 158.6, 142.0, 122.5, 105.8, 97.1, 56.1, 55.5, 42.3, 33.0, 25.5, 22.2; IR (neat) 2935, 1683, 1597 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}O_3$ $[M + H]^+$: 221.1178, found: 221.1151.



3z

4,5,6,7-Tetrahydro-8*H*-cyclohepta[*b*]thiophen-8-one (3z):[235]

Following the general procedure **C**, 5-(thiophen-3-yl)pentanoic acid **1z** (55.3 mg, 0.300 mmol, 1.0 equiv) was converted to 5-(thiophen-3-yl)pentanoyl chloride **2z** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2z** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (90:10 hexanes/EtOAc) afforded **3z** (36.0 mg, 72%) as a colorless oil. The spectral data matched literature values.

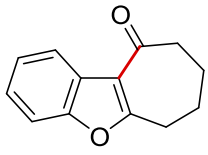


3aa

7,8,9,10-Tetrahydro-6*H*-benzo[*b*]cyclohepta[*d*]thiophen-6-one (3aa):

Following the general procedure **C**, 5-(benzo[*b*]thiophen-3-yl)pentanoic acid **1aa** (70.0 mg, 0.300 mmol, 1.0 equiv) was converted to 5-(benzo[*b*]thiophen-3-yl)pentanoyl chloride **2aa** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2aa** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **3aa** (44.0 mg, 68%) as an off-white solid. Mp 82–83 °C; TLC (50% EtOAc/hexanes) R_f = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.81 (m, 2H), 7.51–7.37 (m, 2H), 3.26–3.13 (m, 2H), 2.96–2.83

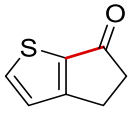
(m, 2H), 2.17–1.94 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 143.3, 141.6, 141.2, 140.1, 127.5, 124.6, 124.0, 123.2, 42.3, 27.1, 25.6, 21.8; IR (neat) 1689, 1616 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}OS$ $[M + H]^+$: 217.0687, found: 217.0693.



3ab

6,7,8,9-Tetrahydro-10*H*-cyclohepta[*b*]benzofuran-10-one (**3ab**):

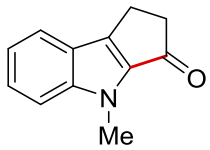
Following the general procedure **C**, 5-(benzofuran-2-yl)pentanoic acid **1ab** (65.5 mg, 0.300 mmol, 1.0 equiv) was converted to 5-(benzofuran-2-yl)pentanoyl chloride **2ab** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2ab** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **3ab** (43.0 mg, 72%) as a colorless solid. Mp 73– 75 °C; TLC (50% EtOAc/hexanes) R_f = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29–8.21 (m, 1H), 7.43– 7.36 (m, 1H), 7.33–7.26 (m, 2H), 3.25–3.15 (m, 2H), 2.91–2.81 (m, 2H), 2.17–2.05 (m, 2H), 2.05–1.95 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.7, 166.2, 153.9, 127.0, 125.0, 124.3, 122.9, 118.3, 110.5, 45.1, 30.1, 24.8, 22.8; IR (neat) 1638, 1580 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}O_2$ $[M + H]^+$: 201.0916, found: 201.0912.



3ac

4,5-Dihydro-6*H*-cyclopenta[*b*]thiophen-6-one (**3ac**)**:**[247]

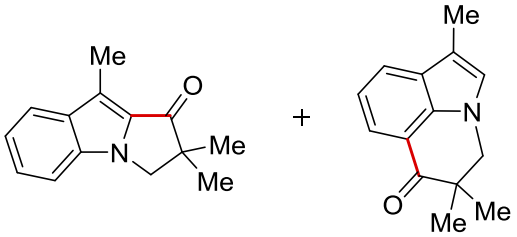
Following the general procedure **C**, 3-(3-thienyl)propanoic acid **1ac** (47.0 mg, 0.300 mmol, 1.0 equiv) was converted to 3-(thiophen-3-yl)propanoyl chloride **2ac** using oxalyl chloride (38.1 μL, 0.450 mmol, 1.5 equiv) in 15 min. The crude acid chloride **2ac** was dissolved in HFIP (1.5 mL) and the resultant reaction mixture was stirred at rt for 16 h. Purification on a Combiflash purification system using a silica flash column (90:10 hexanes/EtOAc) afforded **3ac** (6.00 mg, 14%) as a colorless solid. The spectral data matched literature values.



3ad

4-Methyl-1,2-dihydrocyclopenta[*b*]indol-3(4*H*)-one (3ad):[207,208]

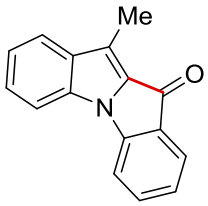
Following the general procedure **C**, 3-(1-methyl-1*H*-indol-3-yl)propanoic acid **1ad** (61.0 mg, 0.300 mmol, 1.0 equiv) was converted to 3-(1-methyl-1*H*-indol-3-yl)propanoyl chloride **2ad** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2ad** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 4 h. Purification on a Combiflash purification system using a 4 g silica flash column (0–30% EtOAc/hexanes over 45 min) afforded **3ad** (39.3 mg, 71%) as a creamish yellow solid. The spectral data matched literature values.



3ae$_2$ **3ae$_7$**

2,2,9-Trimethyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one and 1,5,5-Trimethyl-4,5-dihydro-6*H*pyrrolo[3,2,1-*ij*]quinolin-6-one (3ae$_2$ and 3ae$_7$):

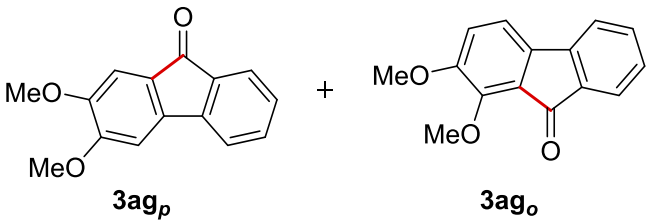
Following the general procedure **C**, 2,2-dimethyl-3-(3-methyl-1*H*-indol-1-yl)propanoic acid **1ae** (69.0 mg, 0.300 mmol, 1.0 equiv) was converted to 2,2-dimethyl-3-(3-methyl-1*H*-indol-1-yl)propanoyl chloride **2ae** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2ae** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (90:10 hexanes/EtOAc) afforded an inseparable mixture of **3ae$_2$** and **3ae$_7$** (50.0 mg, 78%, **3ae$_2$**:**3ae$_7$** = 85:15) as a pale yellow oil. TLC (10% EtOAc/hexanes) R_f = 0.80 (overlapping spots of **3ae$_2$** and **3ae$_7$**). **3ae$_2$**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.74–7.70 (m, 1H), 7.37–7.33 (m, 2H), 7.17 (ddd, *J* = 8.1, 5.7, 2.2 Hz, 1H), 4.15 (s, 2H), 2.58 (s, 3H), 1.39 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.3, 135.2, 132.6, 131.3, 125.3 (2C), 122.2, 120.5, 110.6, 54.6, 50.2, 24.9 (2C), 9.0. **3ae$_7$**: Characteristic peaks only: ^{1}H NMR (400 MHz, $CDCl_3$) 7.77 (dd, *J* = 7.8, 0.9 Hz, 1H), 6.94 (d, *J* = 1.2 Hz, 1H), 4.07 (s, 2H), 2.36 (d, *J* = 1.1 Hz, 3H), 1.30 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 128.7, 125.6, 119.8, 119.5, 116.4, 113.2, 55.8, 43.6, 23.7, 9.9. For the mixture of **3ae$_2$** and **3ae$_7$**: IR (neat) 1698, 1568 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}NO$ $[M + H]^+$: 214.1232, found: 214.1204.



3af

11-Methyl-10*H*-indolo[1,2-*a*]indol-10-one (3af):

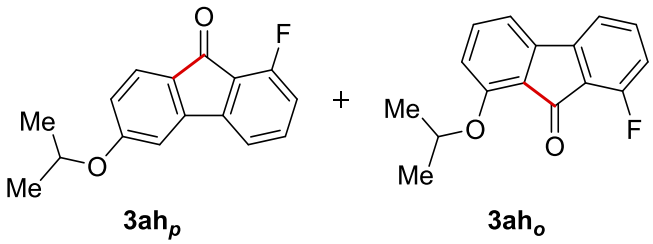
Following the general procedure **C**, 2-(3-methyl-1*H*-indol-1-yl)benzoic acid **1af** (75.3 mg, 0.300 mmol, 1.0 equiv) was converted to 2-(3-methyl-1*H*-indol-1-yl)benzoyl chloride **2af** using oxalyl chloride (33.0 µL, 0.390 mmol, 1.3 equiv) in 50 min (oxalyl chloride was added over 10 min). The crude acid chloride **2af** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 2.5 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–15% EtOAc/hexanes over 30 min) afforded **3af** (60.6 mg, 87%) as an orange-brown solid. Mp 153–156 °C; TLC (2% MeOH/DCM) R_f = 0.62; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (ddd, *J* = 7.5, 1.2, 0.58 Hz, 1H), 7.56 (dt, *J* = 8.0, 0.90 Hz, 1H), 7.46 (td, *J* = 7.8, 1.3 Hz, 1H), 7.43–7.36 (m, 2H), 7.27 (m, 1H), 7.10 (ddd, *J* = 8.1, 6.6, 1.5 Hz, 1H), 7.03 (td, *J* = 7.5, 0.78 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.1, 145.2, 135.2, 134.4, 133.8, 133.0, 130.1, 128.4, 125.0, 123.4, 123.0, 122.5, 121.5, 111.4, 111.2, 9.5; IR (neat) 1678, 1619 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{12}NO$ $[M + H]^+$: 234.0919, found: 234.0901.



3ag$_p$ **3ag$_o$**

2,3-Dimethoxy-9*H*-fluoren-9-one (3ag$_p$) and 1,2-Dimethoxy-9*H*-fluoren-9-one (3ag$_o$):[209]

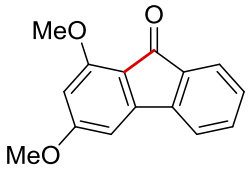
Following the general procedure **C**, 3',4'-dimethoxy-[1,1'-biphenyl]-2-carboxylic acid **1ag** (77.5 mg, 0.300 mmol, 1.0 equiv) was converted to 3',4'-dimethoxy-[1,1'-biphenyl]-2-carbonyl chloride **2ag** using oxalyl chloride (50.8 µL, 0.600 mmol, 2.0 equiv) in 45 min. The crude acid chloride **2ag** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 2.5 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–30% EtOAc/hexanes over 30 min) afforded a complete separation of **3ag$_p$** (65.5 mg, 91%) as an orange solid and **3ag$_o$** (1.50 mg, 2%) as a yellowish orange solid (combined yield = 67.0 mg, 93%; **3ag$_p$**:**3ag$_o$** = 98:2). The spectral data matched literature values.



1-Fluoro-6-isopropoxy-9*H*-fluoren-9-one (3ah$_p$) and 1-Fluoro-8-isopropoxy-9*H*-fluoren-9-one (3ah$_o$):

Following the general procedure **C**, 3-fluoro-3'-isopropoxy-[1,1'-biphenyl]-2-carboxylic acid **1ah** (82.3 mg, 0.300 mmol, 1.0 equiv) was converted to 3-fluoro-3'-isopropoxy-[1,1'-biphenyl]-2-carbonyl chloride **2ah** using oxalyl chloride (50.8 µL, 0.600 mmol, 2.0 equiv) in 45 min. The crude acid chloride **2ah** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 3.5 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–10% EtOAc/hexanes over 40 min) afforded a mixture of **3ah$_p$** and **3ah$_o$** (combined yield = 76.3 mg, 99%; **3ah$_p$**:**3ah$_o$** = 76:24) as a yellow oily solid. For a mixture of products (**3ah$_p$**: **3ah$_o$** = 76:24

by 1H NMR): TLC (15% EtOAc/hexanes) R_f = 0.39; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (**3ah$_p$**; d, *J* = 8.3 Hz, 1H), 7.41–7.34 (**3ah$_p$** and **3ah$_o$**; m, 3H), 7.22 (**3ah$_o$**; d, *J* = 7.4 Hz, 1H), 7.20 (**3ah$_p$**; d, *J* = 7.3 Hz, 1H), 7.05 (**3ah$_o$**; dd, *J* = 7.3, 0.60 Hz, 1H), 6.94 (**3ah$_p$**; d, *J* = 2.1 Hz, 1H), 6.89–6.84 (**3ah$_p$** and **3ah$_o$**; m, 2H), 6.80 (**3ah$_o$**; d, *J* = 8.4 Hz, 1H), 6.69 (**3ah$_p$**; dd, *J* = 8.3, 2.2 Hz, 1H), 4.72–4.59 (**3ah$_p$** and **3ah$_o$**; m, 2H), 1.40 (**3ah$_o$**; d, *J* = 6.1 Hz, 6H), 1.36 (**3ah$_p$**; d, *J* = 6.1 Hz, 6H); ^{13}C NMR (For **3ah$_p$**; 101 MHz, $CDCl_3$) δ 188.9 (d, *J* = 0.97 Hz, 1C), 164.0, 159.1 (d, *J* = 262.4 Hz, 1C), 146.1 (d, *J* = 3.4 Hz, 1C), 145.6 (d, *J* = 3.9 Hz, 1C), 136.4 (d, *J* = 8.4 Hz, 1C), 136.3, 126.46, 121.1 (d, *J* = 12.8 Hz, 1C), 117.8 (d, *J* = 20.9 Hz, 1C), 116.3 (d, *J* = 3.1 Hz, 1C, completely overlapped with **3ah$_o$** peak), 115.2, 108.7, 70.8, 22.1 (2C); (For **3ah$_o$**; 101 MHz, $CDCl_3$) δ 188.0 (d, *J* = 1.2 Hz, 1C), 159.2 (d, *J* = 262.8 Hz, 1C), 157.5, 145.6 (1C, overlapped with **3ah$_p$** peak), 145.5 (d, *J* = 3.7 Hz, 1C), 136.1 (d, *J* = 8.3 Hz, 1C), 126.54, 121.2, 120.4 (d, *J* = 12.4 Hz, 1C), 117.5 (d, *J* = 20.7 Hz, 1C), 117.3, 116.3 (d, *J* = 3.1 Hz, 1C, completely overlapped with **3ah$_p$** peak), 113.3, 72.2, 22.2 (2C); IR (neat; for a mixture of **3ah$_p$** and **3ah$_o$**) 1703, 1619 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}FO_2$ $[M + H]^+$: 257.0978, found for **3ah$_p$**: 257.0940 and found for **3ah$_o$**: 257.0939.

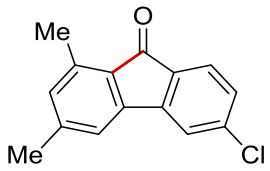


3ai

1,3-Dimethoxy-9*H*-fluoren-9-one (3ai):[210]

Following the general procedure **C**, 3',5'-dimethoxy-[1,1'-biphenyl]-2-carboxylic acid **1ai** (77.5 mg, 0.300 mmol, 1.0 equiv) was converted to 3',5'-dimethoxy-[1,1'-biphenyl]-2-carbonyl chloride **2ai** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 45 min. The crude acid chloride **2ai**

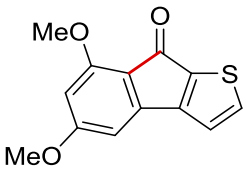
was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 2.5 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–50% EtOAc/hexanes over 25 min) afforded **3ai** (71.5 mg, 99%) as a light yellow solid. The spectral data matched literature values.



3aj

6-Chloro-1,3-dimethyl-9*H*-fluoren-9-one (3aj):

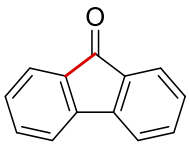
Following the general procedure **C**, 5-chloro-3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid **1aj** (78.2 mg, 0.300 mmol, 1.0 equiv) was converted to 5-chloro-3',5'-dimethyl-[1,1'-biphenyl]-2-carbonyl chloride **2aj** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 45 min. The crude acid chloride **2aj** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 3 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–5% EtOAc/hexanes over 50 min) afforded **3aj** (70.5 mg, 97%) as a light yellow solid. Mp 159.5–161 °C; TLC (15% EtOAc/hexanes) R_f = 0.67; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 1.7 Hz, 1H), 7.17 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.00 (s, 1H), 6.80 (s, 1H), 2.51 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.1, 145.5, 145.2, 143.9, 140.3, 139.7, 133.3, 133.1, 129.0, 128.8, 124.8, 120.5, 119.2, 22.1, 17.8; IR (neat) 1701, 1599 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{12}ClO$ $[M + H]^+$: 243.0577, found: 243.0556.



3ak

5,7-Dimethoxy-8*H*-indeno[2,1-*b*]thiophen-8-one (3ak):

Following the general procedure **C**, 3-(3,5-dimethoxyphenyl)thiophene-2-carboxylic acid **1ak** (79.3 mg, 0.300 mmol, 1.0 equiv) was converted to 3-(3,5-dimethoxyphenyl)thiophene-2-carbonyl chloride **2ak** using oxalyl chloride (50.8 µL, 0.600 mmol, 2.0 equiv) in 60 min. The crude acid chloride **2ak** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 4 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–40% EtOAc/hexanes over 40 min) afforded **3ak** (53.0 mg, 72%) as a yellowish-orange solid. Mp 169.5–172 °C; TLC (30% EtOAc/hexanes) R_f = 0.28; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 4.7 Hz, 1H), 7.00 (d, *J* = 4.7 Hz, 1H), 6.35 (d, *J* = 1.9 Hz, 1H), 6.10 (d, *J* = 1.9 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.3, 166.8, 159.5, 155.0, 143.6, 139.3, 136.8, 119.9, 115.5, 101.5, 96.5, 56.0, 55.9; IR (neat) 1711, 1688, 1616, 1591, 1215, 1130, 1048 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{11}O_3S$ $[M + H]^+$: 247.0429, found: 247.0399.

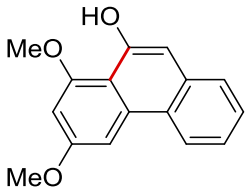


3al

9*H*-Fluoren-9-one (3al):[248,249]

Following the general procedure **C**, 1,1'-biphenyl]-2-carboxylic acid **1al** (59.5 mg, 0.300 mmol, 1.0 equiv) was converted to 1,1'-biphenyl]-2-carbonyl chloride **2al** using oxalyl chloride (50.8 µL,

0.600 mmol, 2.0 equiv) in 45 min. The crude acid chloride **2al** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 4 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–5% EtOAc/hexanes over 50 min) afforded **3al** (6.50 mg, 12%) as a yellow oily solid. The spectral data matched literature values.



3am

6,8-Dimethoxyphenanthren-9-ol (3am):

Following the general procedure **C**, 2-(3',5'-dimethoxy-[1,1'-biphenyl]-2-yl)acetic acid **1am** (82.0 mg, 0.300 mmol, 1.0 equiv) was converted to 2-(3',5'-dimethoxy-[1,1'-biphenyl]-2-yl)acetyl chloride **2am** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2am** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **3am** (50.0 mg, 66%) as a yellow solid. Mp 143–144 °C; TLC (50% EtOAc/hexanes) R_f = 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.47–8.39 (m, 1H), 7.73–7.65 (m, 2H), 7.50 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1H), 7.41 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 6.97 (s, 1H), 6.71 (d, *J* = 2.2 Hz, 1H), 4.09 (s, 3H), 4.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 157.7, 152.2, 135.0, 134.5, 127.5, 126.9, 124.9, 123.4, 123.1, 110.8, 105.7, 98.8, 97.6, 56.7, 55.7; IR (neat) 3327, 1638, 1615 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{15}O_3$ $[M + H]^+$: 255.1021, found: 255.0994.

Chapter 3

Intermolecular Friedel–Crafts acylation reaction promoted by hexafluoro-2-propanol

3.1 Introduction

Friedel–Crafts (FC) acylation is one of the most important reactions in both academia and industry for the synthesis of aromatic ketones.[57,75,250,251] As discussed in the previous chapter, the reaction is promoted by Lewis acids (such as $AlCl_3$, $FeCl_3$, $SnCl_4$, $ZnCl_2$, and $TiCl_4$) or protic acids (such as H_2SO_4).[211,252] FC acylation requires at least a stoichiometric amount of catalyst due to complex formation between product and catalyst.[59] In addition, water workup required in these reactions generates acidic waste. Most existing methods that use catalysts in substoichiometric amounts typically require high temperatures.

The FC acylation products have been utilized for the synthesis of natural products and pharmaceutically useful compounds (Figure 15). For example aryl ketones have been used to prepare the natural products (±)-lacinilene C and aspidospermidine.[253,254] In addition, aryl ketones have been used in synthesis of ibuprofen.[255]

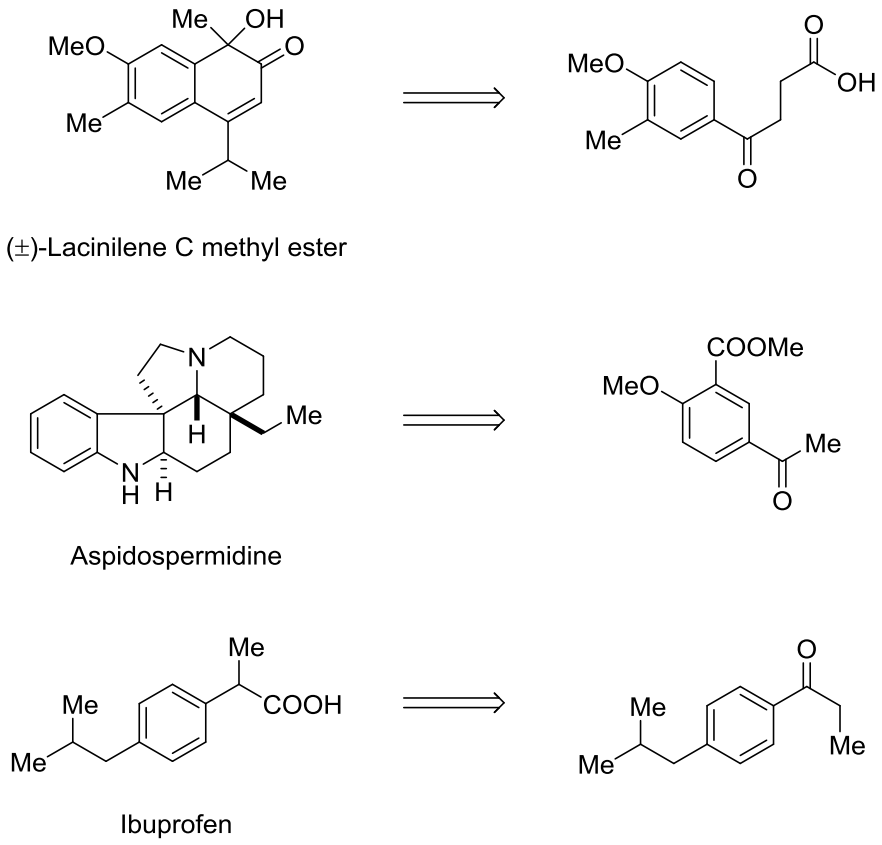


Figure 15. FC acylation in natural products and pharmaceutical compound synthesis.

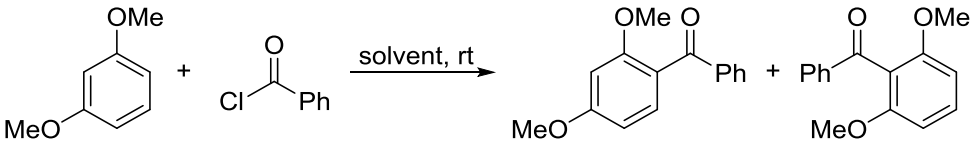
Considering the ease with which the intramolecular FC acylation worked in our methodology, we thought to extend it to a more difficult, intermolecular version of the same reaction.

3.2 Results and discussion

We began by studying the FC acylation reaction between 1,3-dimethoxybenzene (**1a**) and benzoyl chloride (**2a**). To the solution of 1,3-dimethoxybenzene (0.75 mmol, 1.0 equiv) in HFIP, benzoyl chloride (0.75 mmol, 1.0 equiv) was added and the resulting mixture stirred for 5 h at room temperature. Solvent was evaporated and the crude was purified by column chromatography to give **3a**/**3a′** in 66% yield (Table 8, entry 1). The ratio of **3a**/**3a′** was ca. 92:8, which is similar to literature report.[256] When DCM was used as cosolvent, 80:20 HFIP/DCM (corresponding to 10 equiv of HFIP) required to gain yield similar to HFIP alone (Table 8, entries 2–4). As we noticed

in intramolecular version,[173] THF and acetonitrile (H-bond accepting solvents) gave poor results. In the case of THF, in addition to FC products the known THF cleavage 4-chlorobutyl benzoate was obtained (Scheme 22).[257,258]

Table 8. Effect of solvents on yield[a]

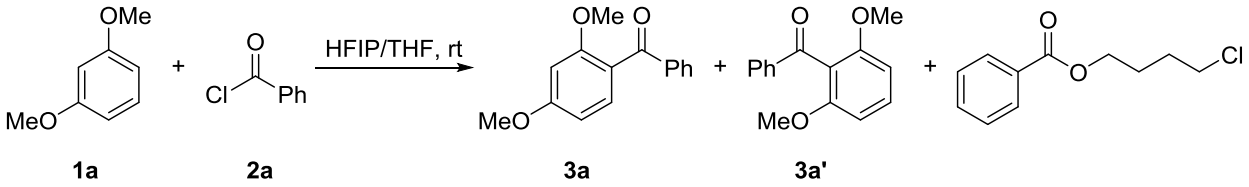


1a **2a** **3a** **3a'**

entry	solvent	Yield (%)[b]
1	HFIP	66
2	8:92 HFIP/DCM[c]	0
3	40:60 HFIP/DCM	39
4	80:20 HFIP/DCM	63
5	80:20 HFIP/THF	16[d]
6	80:20 HFIP/CH_3CN	23
7	CF_3CH_2OH (TFE)[e]	0
8	$(CF_3)_3COH$ (PFTB)[c]	0

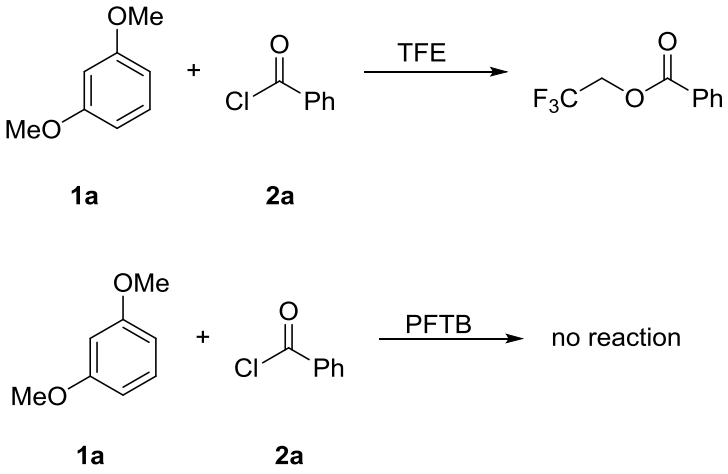
[a]To 1,3-dimethoxybenzene (0.75 mmol, 1.0 equiv) in solvent (1 mL), was added benzoyl chloride (0.75 mmol, 1.0 equiv). The reaction mixture was stirred at rt for 5 h. [b]Isolated yields (**3a**/**3a′** ratios ca. 92:8 in each case). [c]Reaction did not progress. [d]In addition to FC products, 4-chlorobutyl benzoate was obtained in 28% yield. [e]Only TFE ester of benzoyl chloride was observed by GCMS.

Scheme 22. FC acylation using THF as cosolvent



We screened other fluorinated alcohols, trifluoroethanol (TFE) and perfuoro-*tert*-butanol (PFTB), in FC acylation reaction to compare their results with HFIP. However, none of them gave FC products (Table 8, entries 7–8). In TFE, we only observed solvolysis products of benzoyl chloride. On the contrary, in PFTB, both starting materials were observed (Scheme 23).

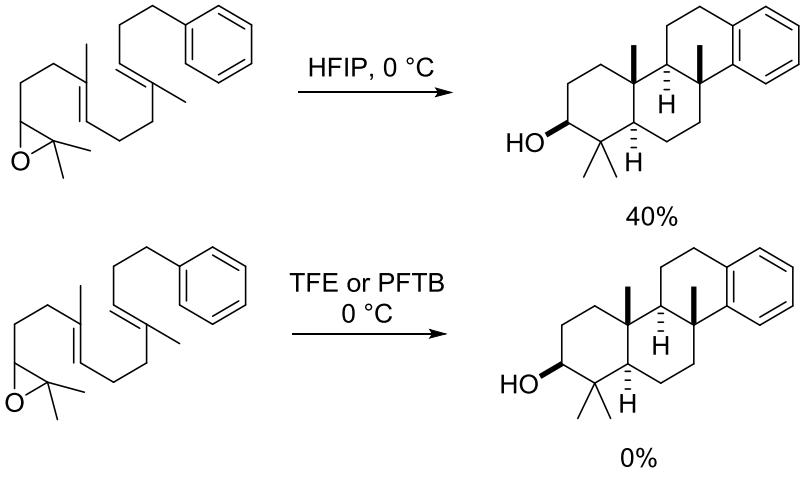
Scheme 23. FC acylation in TFE and PFTB



A similar phenomenon was observed by Qu and coworkers when studying the epoxide-initiated olefin polycyclizations where in HFIP was effective but TFE and PFTB were not (Scheme 24).[259] These data suggest that HFIP has unique properties that promote these reactions and also support the minor role of solvent acidity in promoting these reactions (pKa values: TFE 12.8; HFIP 9.3; and PFTB 5.4[260]) (this finding supported the results obtained in Table 6 of chapter 2, where despite of acidic nature of reagents, they failed to promote FC acylation). Interestingly, PFTB gave

similar results to HFIP in the intramolecular version of FC acylation (Chapter 2, Table 6), which suggests the possibility of activating the acyl halide by coordination with PFTB, but the relative large bulk of solvent might prevent attack by the external nucleophile.

Scheme 24. Fluorinated alcohols in epoxide initiated polycyclizations



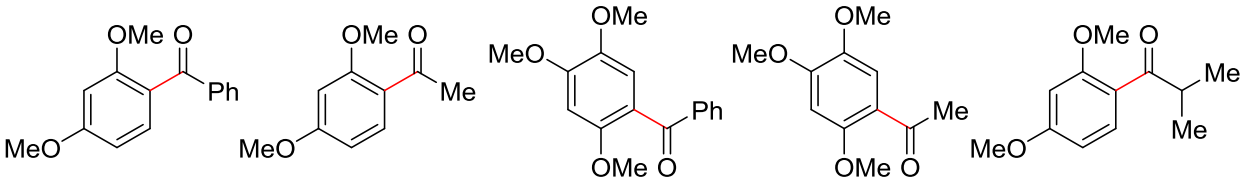
An examination of reaction stoichiometry revealed that best results were obtained when the nucleophilic arene was used in excess, with the optimal ratio being about 3:1 arene/acyl chloride (Table 9, entries 2−4; yields based on acyl chloride). In addition, when benzoyl chloride was added portionwise over a period of 2 h, no change in outcome was noticed (Table 9, entry 5).

Table 9. Further exploration of reaction conditions[a]

entry	**1a** (equiv)	Yield (%)[b] (**3a**/**3a'**)
1	1	66
2	2	80
3	3	84
4	4	80
5[c]	1	66

[a]To 1,3-dimethoxybenzene in HFIP (1 mL), was added benzoyl chloride (0.75 mmol, 1 equiv). The reaction mixture was stirred at rt for 5 h. [b]Isolated yields (**3a**/**3a′** ratios ca. 92:8 in each case). [c]Benzoyl chloride was added in portionwise over a period of 2 h.

The scope of the reaction was explored using the optimized conditions of 3:1 ketone/acyl chloride stoichiometry (Table 9, entry 3). Electron-rich arenes worked well giving product ketones in moderate to good yields (**3a–3i**, Figure 16). Reaction of anisole (singly-activated benzene) with benzoyl chloride resulted **3j** in 34% yield. However, benzene was failed to give FC product **3k** under our conditions. Pyrrole, indoles, and benzothiphenes reacted with acyl chlorides under these conditions to give heteroaryl ketones (**3l–3s**). Ferrocene gave benzoylferrocene **3t** in 62% yield upon reaction with benzoyl chloride.



3a + **3a'** (84%, 91:9) **3b** + **3b'** (81%, 87:13) **3c** (54%) **3d** (60%) **3e** + **3e'** (61%, 99:1)

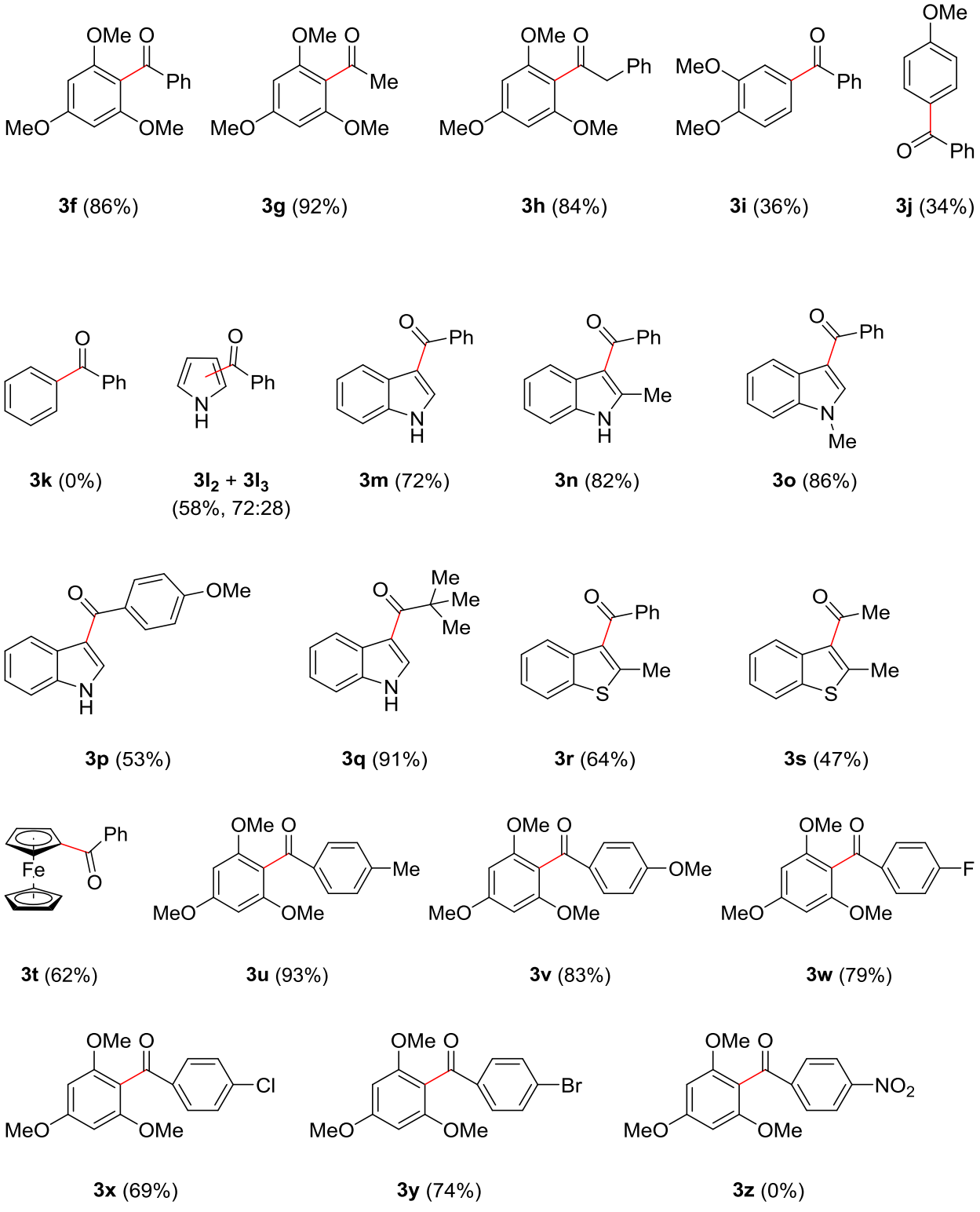


Figure 16. Substrates scope.

Benzoyl chloride with different substituents at the para-position were explored. In FC acylation with 1,3,5-trimethoxybenzene, both containing electron-donating and some electron-withdrawing substituents gave product ketones in good yields (**3u−3y**). Though, reaction of arene and strongly deactivated *p*-NO_2-benzoyl chloride was failed to give product ketone (**3z**).

A common concern of HFIP is that it is expensive, however it can be procured at relatively low prices from specialty vendors ($0.16/g for 1 kg, Oakwood Products, Inc.). In addition, HFIP can be recycled at decagram scale with ease (Figure 17). Using HFIP (12 equiv, 57 mL) as solvent, 1,3,5-trimethoxybenzene **4** (22.7 g, 135 mmol) reacted with benzoyl chloride **2a** (6.33 g, 45 mmol) at rt to yield product ketone **3f** (10.5 g, 86%). HFIP (46 mL) was distilled out directly from the reaction pot and 19 mL of which was further used in reaction between **4** and **2a** to yield 3.80 g of **3f** (93%). HFIP (18 mL) was again distilled out from this reaction and 9.5 mL of which used in third cycle to give 1.85 g of **3f** (91%), allowing recovery of solvent (9 mL). As a result, starting with 57 mL of HFIP, 16.16 g of **3f** was obtained with 45 mL HFIP recovered. In other words, we lost a total of 12 mL of HFIP in this whole process, which was worth ca. $3.17. Moreover, the recovered solvent was as efficient as the store-bought one.

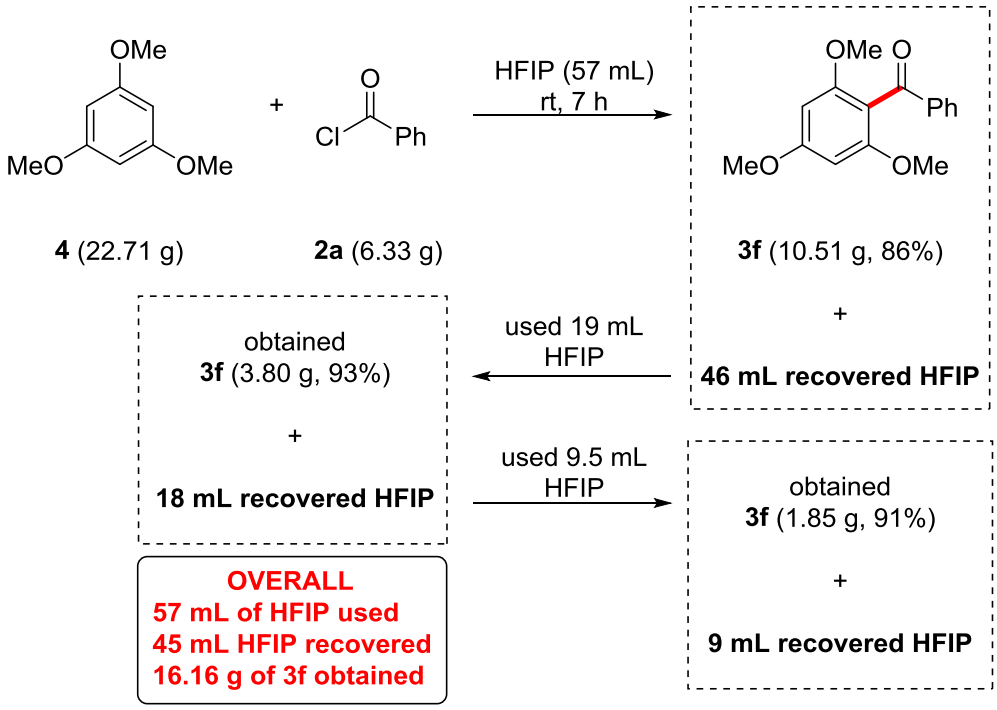


Figure 17. Gram scale reaction.

3.3 Conclusions

In conclusion, we have successfully developed a mild and efficient HFIP promoted intermolecular FC acylation. Electron-rich arenes and heteroarenes gave good results under our conditions. This method is mild and do not require water work up, which is essential in traditional methods. Thus, toxic water waste generation is not a concern with this method.

3.4 Experimental Section

General information. Reactions were performed under an inert atmosphere (argon or nitrogen) in oven-dried glassware. All chemicals were used as received from commercial source without further purification. TLC was performed using commercial glass-backed silica plates (250 microns) with an organic binder. Visualization was accomplished using UV light. Purification was achieved by flash chromatography on a CombiFlash Rf (automated flash chromatography) system.

IR spectra were acquired as thin films or solids. All NMR spectra (^{1}H, ^{13}C) were acquired on either a 400 MHz. Chemical shifts are reported in parts per million (ppm) and are referenced to the center line of the solvent (δ 7.26 and 2.50 ppm with respect to $CDCl_3$ and DMSO-d_6 for ^{1}H NMR and δ 77.16 and 39.52 ppm with respect to $CDCl_3$ and DMSO-d_6 for ^{13}C NMR, respectively). Coupling constants are given in Hertz (Hz). HRMS data were collected with an electrospray ion source (ESI). Allyl bromide intermediates were failed to give HRMS. Melting points were determined on an automated melting point apparatus and are uncorrected.

List of known compounds

(2,4-Dimethoxyphenyl)(phenyl)methanone (**3a**),[261] (2,6-dimethoxyphenyl)(phenyl)methanone (**3a'**),[262] 1-(2,4-dimethoxyphenyl)ethan-1-one **(3b),**[263] 1-(2,6-dimethoxyphenyl)ethan-1-one **(3b'),**[264] phenyl(2,4,5-trimethoxyphenyl)methanone **(3c),**[261] 1-(2,4,5-trimethoxyphenyl)ethan-1-one **(3d),**[264] 1-(2,4-dimethoxyphenyl)-2-methylpropan-1-one (**3e**),[265] phenyl(2,4,6-trimethoxyphenyl)methanone (**3f**),[266] 1-(2,4,6-trimethoxyphenyl)ethan-1-one (**3g**),[267] (3,4-dimethoxyphenyl)(phenyl)methanone (**3i**),[261] (4-methoxyphenyl)(phenyl)methanone (**3j**),[261] phenyl(1*H*-pyrrol-2-yl)methanone (**3l**$_2$),[268] phenyl(1*H*-pyrrol-3-yl)methanone (**3l**$_3$),[269] (1*H*-indol-3-yl)(phenyl)methanone (**3m**),[270] (2-methyl-1*H*-indol-3-yl)(phenyl)methanone (**3n**),[271] (1-methyl-1*H*-indol-3-yl)(phenyl)methanone (**3o**),[272] (1*H*-indol-3-yl)(4-methoxyphenyl)methanone (**3p**),[273] 1-(1*H*-indol-3-yl)-2,2-dimethylpropan-1-one (**3q**),[273] (2-methylbenzo[b]thiophen-3-yl)(phenyl)methanone (**3r**),[274] benzoylferrocene (**3t**),[275] (4-methoxyphenyl)(2,4,6-trimethoxyphenyl)methanone (**3v**),[276] (4-chlorophenyl)(2,4,6-trimethoxyphenyl)methanone (**3x**),[277] 4-chlorobutyl benzoate (**4**).[258] In each case, spectral data obtained was consistent with literature values.

General Procedure for Solvent Screening (Table 8)

To a solution of 1,3-dimethoxybenzene (104 mg, 0.75 mmol, 1.0 equiv) in HFIP and/or specified solvent (1.0 mL) in an oven-dried N_2-flushed 2-dram vial, benzoyl chloride (87 μL, 0.750 mmol, 1.0 equiv) was added. The resultant mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated and crude was purified on a Combiflash purification system using a silica flash column (90:10 hexanes/EtOAc) to afforded **3a/3a'** as a mixture.

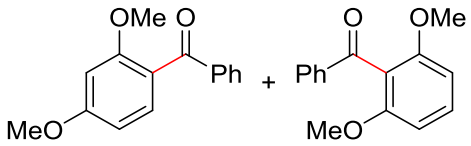
General Procedure for Concentration and Stoichiometry Screening (Table 9)

To a solution of 1,3-dimethoxybenzene (1.0–4.0 equiv as indicated in Table 2) in HFIP (1.0 mL, 0.5 mL or 0.25 mL as indicated in Table 2) in an oven-dried N_2-flushed 2 dram vial, benzoyl chloride (87 μL, 0.750 mmol, 1.0 equiv) was added (for entry 7, total amount of benzoyl chloride was divided into five portions, and each portion was added at 30 min interval over a period of 2 h). The resultant mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated and crude was purified on a Combiflash purification system using a silica flash column (90:10 hexanes/EtOAc) to afforded **3a/3a'** as a mixture.

General Procedure for the Friedel-Crafts reaction in HFIP

To a solution of arenes or heterocyclic arenes (2.25 mmol, 3.0 equiv) in HFIP (1.0 mL) in an oven-dried N_2-flushed 2-dram vial, acid chloride (0.750 mmol, 1.0 equiv) was added. The resultant mixture was stirred at room temperature for 5 h, unless otherwise noted. Reaction mixture was concentrated and crude was purified on a Combiflash purification system using a normal phase silica flash column to afford ketone products.

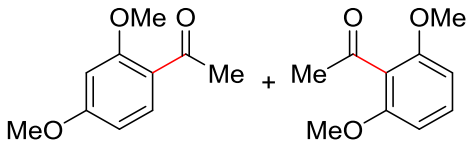
Compound Preparation and Characterization



3a **3a'**

(2,4-Dimethoxyphenyl)(phenyl)methanone (**3a**)[261] and **(2,6-dimethoxyphenyl)(phenyl)methanone** (**3a'**)[262]

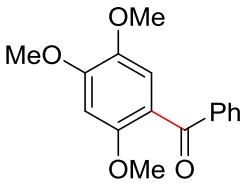
Following the general procedure, 1,3-dimethoxybenzene (311 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μL, 0.750 mmol, 1.0 equiv) to give the known ketones **3a**/**3a'** (152 mg, 84%, **3a**/**3a'** = 91/9) as a mixture.



3b **3b'**

1-(2,4-Dimethoxyphenyl)ethan-1-one (**3b**)[263] and **1-(2,6-dimethoxyphenyl)ethan-1-one** (**3b'**)[264]

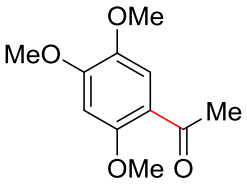
Following the general procedure, 1,3-dimethoxybenzene (311 mg, 2.25 mmol, 3.0 equiv) was reacted with acetyl chloride (53 μL, 0.750 mmol, 1.0 equiv) to give the known ketones **3b**/**3b'** (109 mg, 81%, = 87/13) as a mixture.



3c

Phenyl(2,4,5-trimethoxyphenyl)methanone (3c)[261]

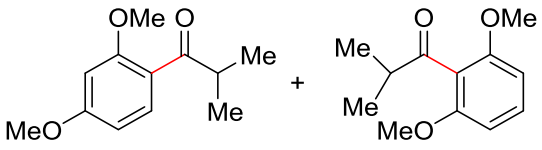
Following the general procedure, 1,2,4-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μL, 0.750 mmol, 1.0 equiv) to give the known ketone **3c** (111 mg, 54%) as a yellow solid.



3d

1-(2,4,5-Trimethoxyphenyl)ethan-1-one (3d)[264]

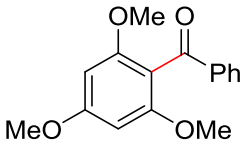
Following the general procedure, 1,2,4-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with acetyl chloride (53 μL, 0.750 mmol, 1.0 equiv) to give the known ketone **3d** (95 mg, 60%) as a white solid.



3e **3e'**

1-(2,4-Dimethoxyphenyl)-2-methylpropan-1-one (**3e**)[265] and **1-(2,6-dimethoxyphenyl)-2-methylpropan-1-one** (**3e'**)

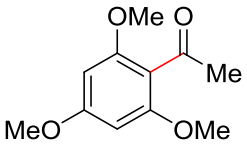
Following the general procedure, 1,3-dimethoxybenzene (311 mg, 2.25 mmol, 3.0 equiv) was reacted with isobutyryl chloride (79 μL, 0.750 mmol, 1.0 equiv) to give the known ketones **3e**/**3e'** (95 mg, 61%, **3e**/**3e'** = 99/1, ratio was determined by GCMS) as a colorless oil.



3f

Phenyl(2,4,6-trimethoxyphenyl)methanone (**3f**)[266]

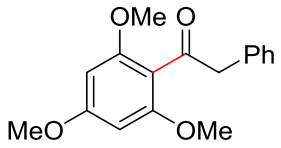
Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μL, 0.750 mmol, 1.0 equiv) to give the known ketone **3f** (176 mg, 86%) as a white solid.



3g

1-(2,4,6-Trimethoxyphenyl)ethan-1-one (**3g**)[267]

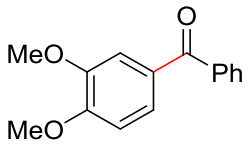
Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with acetyl chloride (53 μL, 0.750 mmol, 1.0 equiv) to give the known ketone **3g** (145 mg, 92%) as a white solid.



3h

2-Phenyl-1-(2,4,6-trimethoxyphenyl)ethan-1-one (**3h**)

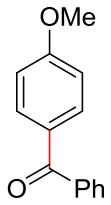
Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with phenylacetyl chloride (99 μL, 0.750 mmol, 1.0 equiv) to give the title ketone (171 mg, 84%) as a yellow solid. Mp 66–68 °C; TLC (20% EtOAc/hexanes) R_f = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37.24 (m, 2H), 7.20 (dt, *J* = 5.8, 1.5 Hz, 3H), 6.06 (s, 2H), 4.03 (s, 2H), 3.80 (s, 3H), 3.73 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.6, 162.5, 158.3, 135.0, 130.0, 128.3, 126.6, 113.3, 90.7, 55.9, 55.5, 51.7. IR (neat) 1698 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{19}O_4$ $[M + H]^+$: 287.1283, found: 287.1280.



3i

(3,4-Dimethoxyphenyl)(phenyl)methanone (**3i**)[261]

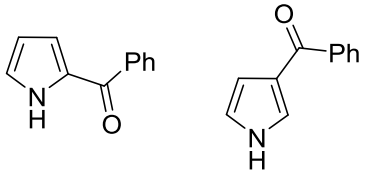
Following the general procedure, 1,2-dimethoxybenzene (311 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μL, 0.750 mmol, 1.0 equiv) to give the known ketone **3i** (73 mg, 36%) as a white solid.



3j

(4-Methoxyphenyl)(phenyl)methanone (**3j**)[261]

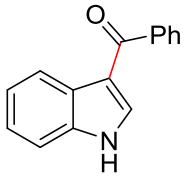
Following the general procedure, anisole (243 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μL, 0.750 mmol, 1.0 equiv) to give the known ketone **3j** (69 mg, 34%) as a colorless oil.



$3l_2$ + $3l_3$
58% (72:28)

Phenyl(1*H*-pyrrol-2-yl)methanone (**$3l_2$**)[268] and **phenyl(1*H*-pyrrol-3-yl)methanone** (**$3l_3$**)[269]

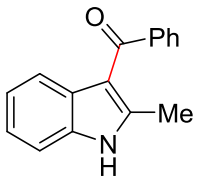
Following the general procedure, pyrrole (151 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μL, 0.750 mmol, 1.0 equiv) to give the known ketones **$3l_2$** (86 mg, 42%) and **$3l_3$** (21 mg, 16%) as a brown solid mixture.



3m

(1*H*-Indol-3-yl)(phenyl)methanone (**3m**)[270]

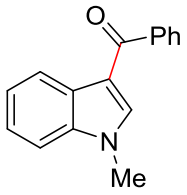
Following the general procedure, indole (264 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μL, 0.750 mmol, 1.0 equiv) to give the known ketone **3m** (119 mg, 72%) as a pale yellow solid.



3n

(2-Methyl-1*H*-indol-3-yl)(phenyl)methanone (**3n**)[271]

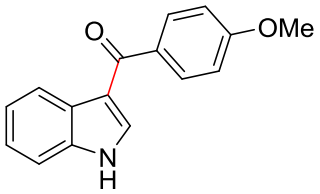
Following the general procedure, 2-methyl-1*H*-indole (295 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μL, 0.750 mmol, 1.0 equiv) to give the known ketone **3n** (144 mg, 82%) as a yellow solid.



3o

(1-Methyl-1*H*-indol-3-yl)(phenyl)methanone (**3o**)[272]

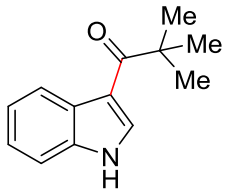
Following the general procedure, 1-methyl-1*H*-indole (295 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μL, 0.750 mmol, 1.0 equiv) to give the known ketone **3o** (152 mg, 86%) as a white solid.



3p

(1*H*-Indol-3-yl)(4-methoxyphenyl)methanone (**3p**)[273]

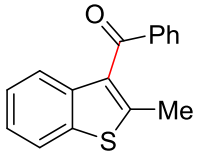
Following the general procedure, indole (264 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-methoxybenzoyl chloride (103 μL, 0.750 mmol, 1.0 equiv) to give the known ketone **3p** (99 mg, 53%) as a brown solid.



3q

1-(1*H*-Indol-3-yl)-2,2-dimethylpropan-1-one (**3q**)[273]

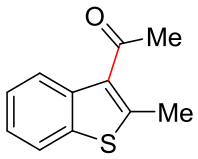
Following the general procedure, indole (264 mg, 2.25 mmol, 3.0 equiv) was reacted with pivaloyl chloride (92 μL, 0.750 mmol, 1.0 equiv) to give the known ketone **3q** (137 mg, 91%) as a brown solid.



3r

(2-Methylbenzo[b]thiophen-3-yl)(phenyl)methanone (**3r**)[274]

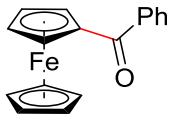
Following the general procedure, 2-methylbenzo[b]thiophene (334 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μL, 0.750 mmol, 1.0 equiv) to give the known ketone **3r** (121 mg, 64%) as a white solid.



3s

1-(2-Methylbenzo[b]thiophen-3-yl)ethan-1-one (**3s**)

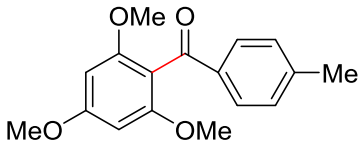
Following the general procedure, 2-methylbenzo[b]thiophene (334 mg, 2.25 mmol, 3.0 equiv) was reacted with acetyl chloride (53 μL, 0.750 mmol, 1.0 equiv) to give title ketone (67 mg, 47%) as a white solid. Mp 66–68 °C; TLC (20% EtOAc/hexanes) R_f = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.75 (ddd, *J* = 8.0, 1.3, 0.7 Hz, 1H), 7.41 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 7.33 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 2.79 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) 196.0, 149.1, 138.5, 137.4, 133.1, 125.3, 124.5, 123.9, 121.8, 32.0, 17.2; IR (neat) 1637 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{11}H_{11}OS$ $[M + H]^+$: 191.0531, found: 191.0529.



3t

Benzoylferrocene (**3t**)[275]

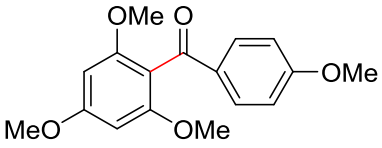
Following the general procedure, ferrocene (419 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μL, 0.750 mmol, 1.0 equiv) to give the known ketone **3t** (135 mg, 62%) as a red solid.



3u

***p*-Tolyl(2,4,6-trimethoxyphenyl)methanone** (**3u**)

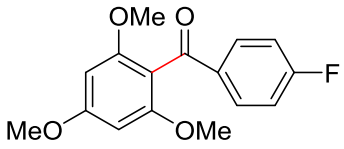
Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-methylbenzoyl chloride (99 μL, 0.750 mmol, 1.0 equiv) to give title ketone (190 mg, 93%) as a white solid. Mp 142–144 °C; TLC (20% EtOAc/hexanes) R_f = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) 7.74 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.17 (s, 2H), 3.86 (s, 3H), 3.68 (s, 6H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.8, 162.4, 158.7, 143.9, 135.9, 129.7, 129.2, 111.3, 90.8, 55.9, 55.6, 21.8; IR (neat) 1655 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{19}O_4$ [M + H]$^+$: 287.1283, found: 287.1279.



3v

(4-Methoxyphenyl)(2,4,6-trimethoxyphenyl)methanone (**3v**)[276]

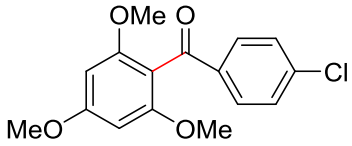
Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-methoxybenzoyl chloride (103 μL, 0.750 mmol, 1.0 equiv) to give the known ketone **3v** (189 mg, 83%) as a white solid.



3w

(4-Fluorophenyl)(2,4,6-trimethoxyphenyl)methanone (**3w**)

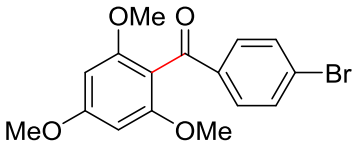
Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-fluorobenzoyl chloride (90 μL, 0.750 mmol, 1.0 equiv) to give title ketone (161 mg, 79%) as a white solid. Mp 152–154 °C; TLC (20% EtOAc/hexanes) R_f = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.81 (m, 2H), 7.11–7.02 (m, 2H), 6.17 (s, 2H), 3.86 (s, 3H), 3.69 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 165.9 (d, $J_{C–F}$ = 255 Hz, 1C), 162.7, 158.8, 134.9 (d, $J_{C–C–C–F}$ = 3 Hz, 1C), 132.2 (d, $J_{C–C–C–F}$ = 9 Hz, 2C), 115.5 (d, $J_{C–C–F}$ = 22 Hz, 2C), 110.7, 90.8, 55.9, 55.6; IR (neat) 1657 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{16}FO_4$ $[M + H]^+$: 291.1033, found: 291.1032.



3x

(4-Chlorophenyl)(2,4,6-trimethoxyphenyl)methanone (**3x**)[277]

Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-chlorobenzoyl chloride (96 μL, 0.750 mmol, 1.0 equiv) to give the known ketone **3x** (140 mg, 69%) as a white solid.

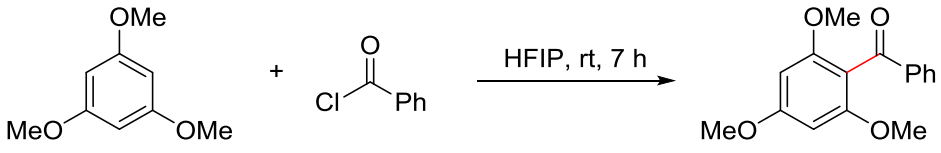


3y

(4-Bromophenyl)(2,4,6-trimethoxyphenyl)methanone (**3y**)

Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-bromobenzoyl chloride (165 mg, 0.750 mmol, 1.0 equiv) to give the title ketone (151 mg, 74%) as a white solid. Mp 188–190 °C; TLC (20% EtOAc/hexanes) R_f = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 6.16 (s, 2H), 3.86 (s, 3H), 3.68 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0, 162.8, 158.9, 137.2, 131.7, 131.1, 128.1, 110.4, 90.8, 55.9, 55.6; IR (neat) 1657 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{16}BrO_4$ $[M + H]^+$: 351.0232, found: 351.0229.

Scale-Up Reactions and HFIP recycling

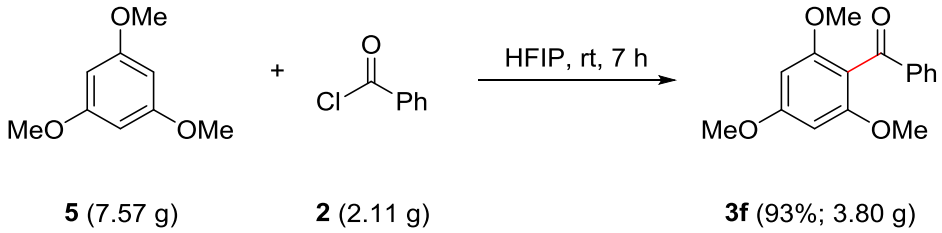


5 (22.71 g) **2** (6.33 g) **3f** (86%; 10.51 g)

Initial reaction:

To a solution of 1,3,5-trimethoxybenzene (22.7 g, 135 mmol, 3.0 equiv) in HFIP (57 mL, 12 equiv) in an oven-dried flask benzoyl chloride (6.33 g, 5.22 mL, 45 mmol, 1.0 equiv) was added. The resultant mixture was stirred at room temperature for 7 h. HFIP solvent was recovered by distillation directly from the reaction pot (40–50 ˚C, under vacuum (5 millibar)) (46 mL, 81%). The remaining product was purified on a Combiflash purification system using solid loading on a silica flash column (80:20 hexanes/EtOAc) to afforded **3f** (10.51 g, 86%) as a white solid.

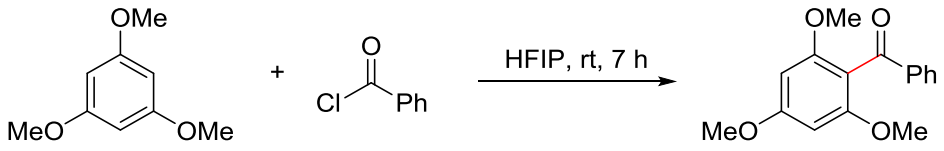
Second reaction, using recovered HFIP



5 (7.57 g) **2** (2.11 g) **3f** (93%; 3.80 g)

To a solution of 1,3,5-trimethoxybenzene (7.57 g, 45 mmol, 3.0 equiv) in HFIP (19 mL, 12 equiv), obtained by distillation from previous reaction, in an oven-dried flask, benzoyl chloride (2.11 g, 1.74 mL, 15 mmol, 1.0 equiv) was added. The resultant mixture was stirred at room temperature for 7 h. HFIP solvent was recovered by distillation as described above (18 mL, 95%). The crude was purified on a Combiflash purification system using a silica flash column (80:20 hexanes/EtOAc) to afforded **3f** (3.80 g, 93%) as a white solid.

Third reaction, using doubly recovered HFIP



5 (3.78 g) **2** (1.05 g) **3f** (91%; 1.85 g)

To a solution of 1,3,5-trimethoxybenzene (3.78 g, 22.5 mmol, 3.0 equiv) in HFIP (9.5 mL, 12 equiv), obtained by distillation from previous reaction, in an oven-dried flask, benzoyl chloride (1.05 g, 0.87 mL, 7.5 mmol, 1.0 equiv) was added. The resultant mixture was stirred at room temperature for 7 h. HFIP solvent was recovered by distillation (9 mL, 95%). The crude was purified on a Combiflash purification system using a silica flash column (80:20 hexanes/EtOAc) to afforded **3f** (1.85 g, 91%) as a white solid.

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